Pediatric Clinical Diagnosis

Diagnostic Approaches of the most common Clinical Presentations

Sixth Edition



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Contents

History and Examination

1. History Taking
2. Clinical Examination

History and Examination

History taking	Physical examination
Personal History Name, age and sex. Address. **Complaint** Main complaint. **Present History** Onset, course and duration. Medications given. Specific questioning. **Past History** Perinatal. Developmental. Nutritional. Vaccination. Infections. **Family History** Parents. Siblings. Significant events.	**Observation** Level of consciousness. Appearance (color). Signs of critical illness. **Vital signs** H.R, R.R, B.P and temperature. **Measurements** Weight, length and head circumference. **Regional examination** Head and neck. Limbs. Skin. Back and spine. Genitalia. **Systemic examination** Neurological examination. Cardiovascular examination. Chest examination. Abdominal examination.

The process of clinical diagnosis depends on 3 basic steps; history taking, physical examination and interpretation of data obtained from history and physical examination to reach the diagnosis.

A) HISTORY TAKING

Accurate relevant history is the most important single factor in making the diagnosis as a large part of information can be derived from it. In infants and young children, history is often obtained from parents or other attendants but older children above 6 years should be encouraged to provide much of the history by themselves.

1. Personal history: It includes the name, sex and age. Birth date should be obtained for proper calculation of age. Residence and nationality are epidemiologically important.

2. Complaint: It includes the main symptom or symptoms that necessitate medical consultation as, for instance, fever, cough, diarrhea, abdominal pain, vomiting, sore throat etc. When parents say that the child is having tonsillitis, bronchitis or arthritis, the doctor should not "swallow" the diagnosis and should ask about the original symptoms, which led to that diagnosis.

3. Present history: It includes the history of present illness, which can be divided into2 components; parent's account and specific questioning. ***Parent's account*** should include the *onset of illness* (acute or gradual), *duration of illness* and *course of illness*. It should also include the *precise order of symptoms* and the *medical attention and medications given*. ***Specific questioning*** is frequently needed by the examiner to clarify the parent's description. These questions vary greatly according to the presenting symptoms. Knowledge and experience are necessary for proper questioning. In the following chapters, the relevant questions will be discussed according to the main presentation.

4. Past history: It includes the history of previous health, which can be divided into perinatal history, developmental history, nutritional history, vaccination history and history of infections. Obviously, the relevance of these histories depends mainly on the age and the clinical presentations.

a) ***Perinatal history:*** Birth history can be divided into prenatal, natal and postnatal history. *Prenatal history* includes maternal illnesses during pregnancy as diabetes or toxemia, maternal medications and x-ray procedures. *Natal history* includes duration of pregnancy, type of labor, birth weight and if any resuscitative measures were required. *Postnatal history* includes the history of any significant illness as low birth weight, convulsions, respiratory difficulty, jaundice, bleeding, fever, vomiting or poor suckling.

b) ***Developmental history:*** It includes the development of motor and mental functions. *Motor development* is assessed by the time at which motor skills are acquired (head support, sitting, standing, walking etc.). Any gross deviation from normal motor development may indicate cerebral palsy, mental retardation or gross environmental neglect as in rickets and malnutrition. *Mental development* is assessed by the time at which intellectual functions are acquired. Social development (in infancy), speech development (in early childhood) and school achievement (in late childhood) are the most useful aspects in evaluating mental development. Gross deviation from normal mental development indicates the presence of mental retardation. Delayed social development in infancy is a sign of severe retardation, while delayed speech in early childhood indicates moderate retardation. School underachievement in late childhood is usually associated with mild retardation.

c) ***Nutritional history:*** It is particularly important in infants and it includes the *type of feeding* (breast, bottle or both), amount/feed, number of feeds/day and concentration of milk. It should also include the onset of *weaning*, foods used and how taken. Nutritional disorders are always associated with dietetic errors as undernutrition (in marasmus) or faulty weaning on low protein diet (in kwashiorkor).

d) ***Vaccination history:*** It is especially important when dealing with infectious diseases. B.C.G. vaccine is usually given at birth. Oral poliomyelitis, D.P.T. (diphtheria, pertussis and tetanus) and hepatitis B vaccine are given at 2, 4 and 6 months. Measles vaccine is given at 9 - 10 months. M.M.R. vaccine (measles, mumps and rubella) may be given at the age of 15 months.

Normal motor development	Normal mental development
During infancy (gross motor skills)	**During infancy (social development)**
At birth: Turns head from side to side.	1 months: Follows moving objects and moving light.
3 months: When held erect, he supports his head.	2 months: Smiles on social contact.
4 months: When held erect, he pushes with feet.	3 months: Listens to music.
5 months: Sits (with full truncal support).	4 months: Laughs loudly and prefers social contact.
6 months: Sits (with pelvic support).	6 months: Recognizes and prefers the mother.
7 months: Sits (without support).	9 months: Responds to own name and says "Mama, Dada".
8 months: Rolls over (turns from prone to supine and reverse).	12 months: Waves "Bye-bye" and plays simple ball game.
9 months: Crawling.	
10 months: Standing.	
12 months: Walks (holding on to furniture).	
15 months: Walks (alone).	
During early childhood (more refined skills)	**During early childhood (speech development)**
1 and 1/2 years: Ascends stairs in a child manner (step by step) and runs stiffly.	1 year: Understands several words but says only 2-3 words.
2 years: Descends stairs in a child manner and runs well.	1and 1/2 years: Says about 10 words.
3 years: Ascends stairs in an adult manner (alternate steps) and can pedal tricycle.	2 years: Knows about 100 words and says a 3 word sentence (telegraphic sentence).
4 years: Descends stairs in an adult manner.	3 years: Gives full name, age and sex.
5 years: Can hop on one foot.	4 years: Tells story, counts up to 10 and recognizes 8 colours.
	5 years: Clear and fluent speech and asks about meaning of words.
During late childhood (fine motor skills)	**During late childhood (school achievement and learning ability)**
Fine hand movements necessary for writing and drawing are acquired. 6 years old child is able to write and to dress himself.	Normal 6 years old child is able to draw a man With all features "Draw-A-Man test".

e) Previous infections: It should include *focal infections* (as CNS, chest, gastro-intestinal, urinary etc.) and *exanthems* (measles, scarlet fever or chickenpox).

f) Previous illnesses or events: Significant illness as allergy or chronic disease and significant events as trauma, operations and accidents should be recorded.

5. Family history: It is especially important in genetic and infectious diseases. It should include the following aspects:

a) Parents: Age, condition of health, consanguinity, occupation and social standard.

b) Siblings: Age, sex, condition of heath and any similar illness.

c) Significant events: History of abortion, stillbirth, previous deaths or congenital anomalies is important in suspected genetic disease. History of acquired chronic illness as allergy, diabetes, rheumatic heart disease and tuberculosis is also important.

B) PHYSICAL EXAMINATION

The examination of infants and children is an art requiring understanding, sympathy and patience. The following rules are helpful while dealing with infants and children:

- **Place of examination:** In late infancy and early childhood, the examining table is frightening to most patients, so examination can be made while the infant or the child is held in the mother's lap or over her chest. Young infants (below 6 months) and older children (above 6 years) can be examined with less difficulty.

- **Sequence of examination:** It is not practical or even desirable to proceed in a precise order. The following rules are helpful:

- Start examination with the system, which is likely to reveal the most useful information and leave to the end the less relevant systems.
- Cardiac and chest examination should be made early and before the patient becomes uncooperative through fear or fatigue.
- Painful procedures as throat and ear examination should be postponed to the end of examination.
- It is important to emphasize that examination should be complete and not limited to the apparently involved system as many abnormalities are asymptomatic and only discovered by routine examination. Congenital heart diseases and abdominal masses are examples.

Examination can be divided into the following aspects:

1. Observation: While taking the history, careful inspection is very useful in detection of several useful information. It should include:

a) ***Level of consciousness (LOC) and activity:*** Conscious, lethargic or comatose?

b) ***Appearance:*** Abnormal findings as pallor, cyanosis or jaundice should be observed.

c) ***Evidence of critical illness:*** Respiratory distress (rapid respiration, working alae nasi and grunting), dehydration (sunken eyes) and toxic face should be observed.

d) ***Other findings:*** Abnormal features (as in mongolism), edematous face (as in nephrotic syndrome), wasting and cachexia (as in chronic infections and malignancy) and facial rash (as in measles) can be easily detected.

2. Vital signs: Temperature, respiratory rate, heart rate and blood pressure are very essential data in examination of every patient.

a) ***Temperature:*** Normal rectal temperature is around 37.0 - 37.5°C. *Fever* is a rectal temperature above 37.8°C, while temperature below 35.5°C denotes *hypothermia.*

b) ***Respiratory rate:*** Normal respiratory rate varies with age (see below). It is important to count the respiratory rate over a full minute and in quiet patient. *Tachypnea* (rapid respiration) is the first sign of respiratory distress.

c) ***Heart rate:*** Normal heart rate varies also with age (see below). It is also important to count the heart rate over a full minute and in quiet patient. Crying, may elevate the heart

rate in an infant to values above 200 /minute. *Tachycardia* (rapid heart rate) disproportionate to age and body temperature may denote the presence of shock or heart failure.

d) Blood pressure: It should be measured at least in renal and cardiovascular conditions Normal values vary with age (see below). For proper measurement, the appropriate size of the cuff should be used (see hypertension). Both *hypertension* and *hypotension* are serious problems that should not be overlooked.

Normal respiratory rate, heart rate and blood pressure at different ages

Age	Respiratory rate	Heart rate	Blood pressure
Newborns	40 (35-45)	120 (90 - 150)	80/50
Infants	30 (25-35)	110 (80-140)	80/50
Young children	25 (20-30)	100 (80-120)	85/55
Old children	20 (15-25)	80(70-110)	90/60

Notice: Each degree rise in body temperature increases the respiratory rate about 5 breaths/minute and heart rate about 10 beats/minute

3. Measurements: Weight, length (or height) and head circumference are important aspects of physical growth that should be measured in every case. As there is a wide range of variations among normal children, growth curves were designed to differentiate between normal and abnormal growth. *Growth curves* are available in percentile values where 50th percentile represents the average and indicates that 50% of normal children are below this value. 25th, 10th and 5th percentile are low normal values while 75th, 90th and 95th are high normal values. Values below 5th percentile or above 95th percentile are abnormal.

Abnormalities in physical growth

Parameter	Below 5th percentile	Above 95th percentile
Weight	Underweight	Overweight
Length (height)	Short stature	Tall stature
Head circumference	Small head	Large head

4. Regional examination: Several relevant abnormalities can be detected by routine examination It should include the following aspects:

a) Head and neck: Examination should include the following areas:

(i) Anterior fontanel: The size of anterior fontanel at birth is about 3 fingers breadth. However, a range of 1 - 5 fingers is normal. It is 2 fingers at 6 months, 1 finger at one year and it normally closes at the age of one and half years (normal closure may range between 6 - 24 months). In spite of these limitations, several relevant information can be obtained.

Average weight for age

At birth: 3 kg
During the first 4 months, weight gain is about 750 gm/month.
1 month: 3.750 kg
2 months: 4.500 kg
3 months: 5.250 kg
4 months: 6.000 kg (2 times birth weight)
During the second 4 months, weight gain is about 500 gm/month.
5 months: 6.500 kg
6 months: 7.000 kg
7 months: 7.500 kg
8 months: 8.000 kg
During the third 4 months, weight gain is about 250 gm/month.
9 months: 8.250 kg
10 months: 8.500 kg
11 months: 8.750 kg
12 months: 9.000 kg (3 times birth weight)
During early childhood, weight gain is about 2 kg/year.
2 years: 12 kg
3 years: 14 kg
4 years: 16 kg
5 years: 18 kg
6years: 20 kg
During late childhood, weight gain is about 2.5 kg/year.
7 years: 22.5 kg
8 years: 25 kg
9 years: 27.5 kg
10 years: 30 kg (10 times birth weight)

Average length or height for age

At birth: 50 cm
6 months: 68 cm
1 year : 75 cm
2 years: 87 cm
3 years: 94 cm
4 years: 100 cm (2 times birth length).
Between 4 - 8 years, the height increases about 7 cm/year.
5 years: 107 cm
6 years: 114 cm
7 years: 121 cm
8 years: 128 cm
Between 8 - 12 years, it is about 5 cm/year.
9 years: 135 cm
10 years: 140 cm
11 years: 145 cm
12 years: 150 cm (3 times birth length).

Average head circumference for age

At birth: 35 cm
At 6 months: 43 cm
1 year : 47 cm (4 cm more)
2 years: 49 cm (2 cm more)
6 years: 51 cm
12 years: 53 cm

(ii) Face: Examination may reveal abnormal features (as in Mongolism or cretinism), facial edema (as in nephrotic syndrome), facial wasting (as in marasmus), facial paralysis or parotid swelling.

(iii) Eyes: Examination may reveal jaundice, conjunctival hemorrhage or cataract. Eye examination should include evaluation of vision and pupillary size and reaction to light (see also neurological examination and comatose child).

(iv) Ears: Examination may reveal anomalies as malformed or low set ears. Examination of the eardrum by an otoscope should be a routine step in every patient.

(v) Mouth and throat: Examination may reveal angular stomatitis, mouth ulceration or pharyngitis. Mouth examination should also include teeth examination. Most causes of widely patent fontanel are also associated with delayed teething.

(vi) Neck: Examination may reveal engorged pulsating neck veins, cervical lymph node enlargement or thyroid swelling.

Value of examination of anterior fontanel

Bulging fontanel
Increased intracranial pressure.
Sunken fontanel
Dehydration

Widely patent fontanel
Rickets and achondroplasia
Trisomies as Trisomy 21
Congenital hypothyroidism
Congenital hydrocephalus

Delayed closure.
Same causes of patent fontanel

Early closure
Craniostenosis

Approximate time of teeth eruption

Primary (milk) teething (20 teeth)

Central incisor :	6 months
Lateral incisor	9 months
First molar:	12 months
Canine:	18 months
Second molar:	24 months

Secondary (permanent) teething (32 teeth)

First molar:	6 years
Central incisor:	7 years
Lateral incisor:	8 years
Canine:	9 years
First premolar:	10 years
Second premolar:	11 years
Second molar:	12 years
Third molar:	18 years

b) Upper and lower limbs: Examination may reveal edema, clubbing of fingers (pale or blue), deformities or anomalies as polydactyly or syndactyly.

c) Skin: Examination may reveal maculopapular rash (as measles), vesicular rash (as chikenpox), purpuric eruption or skin changes of kwashiorkor.

d) Back and spine: Examination may reveal angular deformity (as in Pott's disease), kyphosis, lordosis or scoliosis, swelling as meningocele or meningomyelocele.

e) Genitalia: Examination of genitalia should be a routine step, especially in males. Examination may reveal ambiguous genitalia, hypospadius, undescended testis, scrotal swelling as hydrocele or inguinal hernia. Serious conditions as strangulated inguinal hernia or torsion of undescended testis should not be overlooked.

5. Systemic examination: It includes neurological, cardiac, chest and abdominal examination.

a) Neurological examination: It includes evaluation of the level of consciousness (LOC), mentality, head examination, motor, sensory and autonomic functions.

b)Cardiovascular examination: Evaluation of cardiovascular function should start with observing relevant extracardiac signs as cyanosis, peripheral perfusion, femoral pulsations and features of acute or chronic congestive heart failure. Actual cardiac examination is made by inspection, palpation, percussion and auscultation.

c) Chest examination: Before actual chest examination, attention should be given at abnormal audible sounds as cough and noisy respiration. Actual chest examination is made by inspection, palpation, percussion and auscultation.

d) Abdominal examination: It includes inspection, palpation, percussion, auscultation.

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Neonatology

- Neonatal Examination.
1. Low Birth weight Baby.
2. Neonatal Convulsions.
3. Neonatal Respiratory Distress.
4. Neonatal Jaundice.
5. Neonatal Sepsis or Septicemia.
6. Neonatal Vomiting.
7. Neonatal Bleeding.
8. Neonatal Anemia.
9. Neonatal Crying.
10. Neonatal Cutaneous Lesions.

Neonatal Examination

Quick examination to detect critical conditions

Apgar score (immediately after birth at 1, 5, 10, 15 and 20 minutes), then
Level of consciousness and activity
Color (appearance)
Vital signs (heart rate, respiratory rate and temperature)

Detailed examination

Measurements (weight, length and head circumference)
Regional examination (head, limbs, skin, back and genitalia)
Systemic examination (neurological, cardiac, chest and abdominal)

Special examination for peculiar neonatal problems

Prematurity (assessment of gestational age)
Congenital anomalies
Birth injuries

A) QUICK EXAMINATION

Apgar score is a simple and practical method to assess the condition of the newborn immediately after birth. The score assesses 5 variables and each one takes a score of zero, one or two (total score is 10). The score is made initially at 1 minute to discover newborns who are depressed and are in need of resuscitation, then it is repeated at 5, 10, 15 and 20 minutes to evaluate how resuscitation was successful. Low score at 20 minutes is associated with high mortality and serious neurological sequelae.

Apgar score

Sign	0	1	2
Heart rate	Absent	below 100	Above 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Good flexion
Response to catheter in nostril	No response	Some motion	Cough, sneeze
Color	Blue, pale	Body pink, limbs blue	All pink

- **High score (10 - 8):** Good condition. Routine care.
- **Moderate score (7- 4):** Mild to moderate depression. Simple resuscitative measures as suction, oxygen and manual ventilation with bag and mask.
- **Low score (3 - 0):** Severe depression. Vigorous resuscitative measures including endotracheal intubation, assisted ventilation and drug therapy.

Beyond the immediate postnatal period, quick examination can be made by assessing the level of consciousness and activity, color (appearance) and vital signs.

1. Level of consciousness and activity: Normal newborn is conscious and active and he responds to stimulation by crying or active movements. He has a good suckling power.

a) Disturbed consciousness as lethargy or coma indicates a serious cerebral lesion or severe infection. Convulsions and/or increased intracranial pressure (bulging fontanel) may be also present (see neonatal convulsions).

b) Poor or absent suckling also denotes a serious illness as intracranial hemorrhage or severe infection. In fact, evaluation of suckling power is the most important single test in examination of the newborn. Good suckling indicates a good general condition, while poor or absent suckling denotes a serious illness.

2. Color (appearance): Normal newborn is pinkish in color. Abnormal findings include:

a) Pallor: It indicates hypoxia, shock or anemia.

b) Central cyanosis: It indicates a serious brain lesion, severe pulmonary disease or congenital cyanotic heart disease. Hematological conditions (as polycythemia) and metabolic conditions (as hypoglycemia) may be also responsible. Clinical differentiation between different causes depends mainly on the level of consciousness and respiratory pattern:

Diagnostic clues of neonatal cyanosis

System affected	Diagnostic clue
Brain lesion	Disturbed consciousness, ± convulsions and increased ICP. Respiratory depression (slow irregular respiration).
Severe pulmonary disease	Respiratory distress (tachypnea, retractions, grunting).
Congenital CHD (with heart failure)	Respiratory distress. Triad of tachycardia, tachypnea and enlarged tender liver.
Congenital CHD (without heart failure)	Normal respiration and normal consciousness. ± Heart murmurs.
Polycythemia	Plethora, ± respiratory distress. Hematocrit value above 65%.
Hypoglycemia	± Disturbed consciousness, heart failure. Blood sugar below 30 mg/dl. Responds to I.V. glucose.

CHD: Cyanotic heart disease. **ICP:** Intracranial pressure

i) Central cyanosis with normal consciousness and normal respiration is mostly due to congenital cyanotic heart disease. Cyanosis becomes more intense with crying and it is not relieved with 100% oxygen.

(ii) Central cyanosis with disturbed consciousness and respiratory depression (slow irregular shallow respiration) usually indicates a serious brain lesion as hypoxic ischemic encephalopathy or intracranial hemorrhage.

(iii) Central cyanosis with respiratory distress (rapid respiration, retractions and grunting) is mostly caused by severe pulmonary disease. Congenital cyanotic heart disease with congestive heart failure should be also considered.

(iv) Measurement of hematocrit value and blood sugar level should be a routine to exclude polycythemia and hypoglycemia.

c) Plethora: It usually indicates polycythemia, which may lead to respiratory distress and cyanosis. Diagnosis is confirmed by presence of hematocrit value above 65.

d) Jaundice: It is a common problem, which may be physiological or pathological. Diagnosis of the cause of jaundice depends on the onset and type of hyperbilirubinemia.

3. Vital signs: Normal newborn has a heart rate of about 120 - 140/minute, respiratory rate of around 40/minute and a temperature of 36.5 - 37.5°C. Abnormalities in vital signs include:

a) Tachycardia (heart rate above 180/minute in a quiet baby) may indicate hypoxia or heart failure. ***Bradycardia*** (heart rate below 80/minute) usually indicates hypoxia.

b) Tachypnea (respiratory rate above 60/minute) is the first sign of respiratory distress and may be caused by pulmonary, cardiac or metabolic conditions (see neonatal respiratory distress). ***Slow, shallow and irregular breathing*** (respiratory depression) is usually associated with serious brain lesions as hypoxic ischemic encephalopathy or intracranial hemorrhage. ***Recurrent apnea*** (cessation of respiration for more than 20 seconds and is significant when it is associated with bradycardia and/or cyanosis) is common in very low birth weight infants (below 1500 gm) and in several other conditions.

c) Fever (rectal temperature above 38.0°C) is caused by high environmental temperature (overheated infant) or true fever (febrile infant). *Overheated infant* looks healthy, pink with warm hands and feet while *febrile infant,* on the other hand, looks unwell, pale with cool hands and feet. Serious infections (septicemia, pneumonia and meningitis) and cerebral abnormalities (birth asphyxia, holoprocencephaly and encephalocele) are the main causes of true fever. Hyperpyrexia (rectal temperature above 41.0°C) is invariably caused by overheating. ***Hypothermia*** (rectal temperature below 35.5°C) is mainly caused by low environmental temperature (cold exposure). Other causes include severe prematurity, bacterial sepsis, severe heart failure and drugs given to the mother especially sedatives as diazepam. Hypothermia may be mild (35.5° -34.0°C), moderate (34.0 - 30.0°C) or severe (below 30.0°C). Moderate to severe hypothermia is associated lethargy, poor feeding, poor activity and weak cry.

Causes of neonatal recurrent apnea

System affected	Causes
CNS disorders	Hypoxic ischemic encephalopathy, intracranial hemorrhage, kernicterus. Drugs.
Respiratory	Hyaline membrane disease, pneumonia, aspiration, pneumothorax. Airway obstruction.
Infections	Septicemia, meningitis, necrotizing enterocolitis.
Metabolic	Hypoglycemia, hypomagnesemia, hyponatremia, hypernatremia, acidosis, hypothermia, hyperthermia.
Cardiovascular	Hypovolemia, hypotension, anemia, heart failure.
Gastrointestinal	Oral feeding, esophagitis, intestinal perforation.
Apnea of prematurity	Diagnosis is by exclusion of above conditions, mainly in very low birth weight infants and in those with gestational age below 32 weeks.

Persistent severe hypothermia is serious and it leads to facial edema, sclerema (skin hardening), ileus and even death. Rewarming over few hours using a radiant warmer or an incubator should be carried out.

B) DETAILED EXAMINATION

Thorough and complete examination includes measurements, regional examination and systemic examination.

1. Measurements: A normal newborn has approximately a weight of 3 kg, length of 50 cm and head circumference of 35 cm. Abnormal measurements include:

a) Low birth weight (below 2500 gm) is caused by prematurity, intrauterine growth retardation (small for gestational age) or both conditions. ***High birth weight*** (weight above 4000 gm) is usually seen in infants of diabetic mothers.

b) Small head is caused by congenital microcephaly, chromosomal anomalies and congenital infections. ***Large head*** mostly indicates congenital hydrocephalus.

2. Regional examination: The same items mentioned in general history and examination are applied. Relevant abnormal findings include:

a) Head and neck: Look for birth trauma (as caput succedaneum or caphalohematoma), bulging anterior fontanel, abnormal features (as Mongolism), eyes (cataract or subconjunctival hemorrhage), ears (malformed or low-set ears), nose (choanal atresia) and mouth (cleft lip or palate and oral moniliasis).

b) Limbs: Look for birth trauma (as Erb's palsy or fractures) and for congenital anomalies as talipes equinovarus, polydactyly or syndactyly. Special examination for congenital dislocation of the hip is important (see below).

c) Skin: *Meconium staining* of the skin and cord is an important sign of fetal distress.

Skin mottling may indicate poor peripheral perfusion and shock. *Generalized edema* at birth (hydrops fetalis) is mostly caused by a severe hemolytic disease especially when associated with intense pallor. *Sclerema* (skin hardening) is an ominous sign, which is associated with very high mortality rate especially in very low birth weight babies who were subjected to cold injury. Skin examination should include a search for lacerations and rashes especially in the napkin area as napkin dermatitis is quite common.

d) Back and spine: It is important to look for vertebral defects or swellings as meningocele (covered with skin) or meningomyelocele (covered with thin membrane).

e) Genitalia: Examination of genitalia should be a routine step in neonatal examination. Ambiguous genitalia (genitalia in which the sex can not be determined) is a medical emergency. It may represent an underdeveloped male genitalia or overdeveloped female genitalia. In males, hypospadius and undescended testes should be excluded. Scrotal swellings as congenital hydrocele are common.

3. Systemic examination: It includes examination of the main 4 systems (neurological, cardiac, chest and abdominal).

a) Neurological examination: After evaluation of the level of consciousness and activity, 2 other points are left: muscle tone and neonatal reflexes.

(i) Muscle tone (posture): A normal newborn has a posture of complete flexion (flexion of four limbs). Frog-leg position indicates severe hypotonia.

(ii) Neonatal reflexes: There are 2 types of reflexes: tendon reflexes and primitive reflexes. Tendon reflexes as knee and ankle jerks are normally present. Primitive neonatal reflexes are a group of reflexes peculiar to neonatal period and early infancy. Eliciting these reflexes is important for several reasons:

(1) Evaluation of the general condition: Normal response indicates a good neurological condition while poor or absent response is associated with general neurological depression as in hypoxic ischemic encephalopathy and intracranial hemorrhage. Suckling reflex and Moro reflex are the most useful reflexes in evaluation of the general condition.

(2) Evaluation of vision and hearing: Optic blink and acoustic blink are useful in evaluation of vision and hearing of the newborn.

(3) Detection of focal lesions: Asymmetric response is usually associated with a focal lesion. In Erb's palsy, fracture clavicle or septic arthritis, asymmetric Moro reflex, grasp reflex or withdrawal reflex are usually evident. Also in patients presenting with convulsions and disturbed consciousness, asymmetric response, especially in pupillary reaction to light, is very suggestive of intracranial hemorrhage.

(4) Assessment of gestational age: The time of appearance of some reflexes can be useful in assessment of gestational age. Glabellar reflex and grasp reflex are particularly important (see low birth weight baby).

(5) Persistence of some reflexes as Moro reflex and grasp reflex beyond the age of 4 months may indicate cerebral palsy especially when it is associated with hypotonia or spasticity.

Primitive neonatal reflexes

Reflex	How elicited	Significance
1. Cranial nerve reflexes		
• **Optic blink** (II)	Sudden exposure of eyes to bright light leads to blinking	Important for evaluation of vision
• **Pupillary reflex** (II, III and V)	Exposure of the eyes to bright light leads to pupillary constriction.	Asymmetric response indicates a focal lesion
• **Doll's eye** (III, IV and VI)	When turning the head slowly to right or left, the eyes do not move with the head.	Disappears at 2 weeks and abnormally appears in comatose patients.
• **Rooting** (V)	With light contact to the cheek, the infant turns towards the point of contact.	It represents a physiological searching for the nipple.
• **Glabellar** (V, VII)	Tapping of the forehead leads to eye closure.	Important in assessment of gestational age.
• **Acoustic blink** (VIII)	Clapping the hands near the infant's head leads to motor response (Moro).	Important for evaluation of hearing.
• **Suckling & swallowing** (IX, X and XI)	On feeding, suckling and swallowing normally occur.	Absent reflexes indicates a serious brain lesion or serious infection.
2. Cutaneous reflexes		
• **Grasp or palmar reflex**	If you put your finger in the infant's palm, he grasps it.	Important in assessment of gestational age and detection of focal lesions.
• **Withdrawal reflex**	On pricking the sole of the foot with a pin, rapid flexion of the hip, knee and foot occurs.	Important in detection of focal lesions.
3. Extensor reflexes		
• **Moro reflex**	Sudden noise or sudden drop of the head for few centimeters results in abduction and extension of arms followed by adduction and flexion.	Absent reflex indicates a serious brain lesion. Asymmetric response is observed in focal lesions as Erb's palsy.
• **Tonic neck reflex**	Rotating the neck to one side results in increased tone and partial extension of the arm and leg on the side to which the head is rotated.	Same significance of Moro reflex.
4. Progression reflexes	(walking reflex, placing reflex) are of little significance.	

b) Cardiac examination: After counting the heart rate in quick examination, 3 other points are important:

(i) Apex beat: Normally, the maximal intensity of the apex beat is in the left 4th intercostal space just outside the mid-clavicular line. Apex beat to the right of the sternum indicates dextrocardia or a left sided pathology pushing the heart to right as in pneumothorax or diaphragmatic hernia.

(ii) Cardiac murmurs: More than 90% of murmurs heard at birth are innocent transient murmurs that will disappear over few days or weeks and only less than 10% of murmurs represent a congenital heart disease. It should be noted, on the other hand, that murmurs which are not present at birth and appear later in neonatal period or early infancy are mostly representing a congenital heart disease. Significant persistent murmurs necessitate further evaluation including chest x-ray, ECG and echocardiography.

(iii) Femoral pulsations: Palpation of femoral pulsations should be a routine step. A weak or absent pulsations should suggest coarctation of aorta.

Clinical presentations of neonatal cardiac disease

Presentation	Causes
Central Cyanosis	Congenital cyanotic heart disease (after exclusion of other causes) Chest x-ray, ECG and echocardiography are necessary.
Cardiac murmurs	Innocent (90%) or congenital heart disease (10%). Persistent significant murmurs necessitate further evaluation.
Congestive heart failure	Congenital cyanotic heart disease. Congenital noncyanotic heart disease. Myocardial ischemia. Arrhythmias.
Apex beat to the right	Dextrocardia (isolated or with situs inversus).
Absent femoral pulsations	Coarctation of aorta.

c) Chest examination: After counting the respiratory rate in quick examination, 3 other points are important:

(i) Rhythm of breathing: A normal newborn has a regular breathing with no apneic spells. Apnea (cessation of respiration for more than 20 seconds with or without cyanosis and bradycardia) is present in prematurity and other several pathological conditions.

(ii) Pattern of breathing: A normal newborn has a breathing of normal rate and adequate chest expansion. Abnormalities include respiratory distress and respiratory depression. In respiratory distress, the respiration is rapid and may be associated with intercostal and subcostal retractions and expiratory grunting. In respiratory depression, respiration is slow and shallow (hypoventilation) and is commonly associated with disturbed

consciousness and may be cyanosis (see neonatal respiratory distress).

(iii) Chest auscultation: Thorough examination of the chest is important to differentiate between different causes of respiratory distress.

d) Abdominal examination: The abdomen of a normal newborn is slightly distended and lax. The liver may be normally palpated just below the costal margin. Relevant signs on examination are:

(i) Abdominal distension: Observed in severe septicemia or intestinal obstruction.

(ii) Organomegaly: Hepatomegaly and/or splenomegaly should suggest congenital infections or metabolic disease.

(iii) Retracted or scaphoid abdomen should suggest diaphragmatic hernia.

(iv) Umbilical examination: Umbilical sepsis, umbilical granuloma or hernia, are all common problems that should not be overlooked.

C) SPECIAL EXAMINATION

Special attention should be given to peculiar neonatal problems especially prematurity, congenital anomalies and birth injuries.

1. Signs of prematurity: A ***normal newborn*** has a well developed sole creases, normal genitalia (descended testes in males and prominent labia majora in females), normal breast nodule *(0.5* cm in diameter), well-formed cartilaginous ear lobule and coarse silky hair. A ***premature baby*** has incomplete sole creases, underdeveloped genitalia (undescended testes in males and prominent labia minora in females), small breast nodule (less than 3 mm), shapeless and pliable ear lobule and fine woolly scalp hair. Assessment of gestational age and degree of low birth weight is important (see low birth weight baby).

2. Congenital anomalies: Several anomalies can be recognized at birth or in neonatal period. Anomalies can be superficial and evident (as abnormal features, limb defects or hernias) or hidden (as cardiac or renal anomalies). Clinically, a complete "head-to-toe" examination is important taking into consideration the early detection of life-threatening anomalies. Common anomalies are:

a) Head anomalies: Hydrocephalus, microcephaly, encephalocele and abnormal features as Mongolism (see genetics, odd-looking face).

b) Limb anomalies: Short limbs, polydactyly, syndactyly or talipes can be easily recognized: Special attention should be given to *congenital dislocation of the hip.* With the hips and knees flexed at right angles, the thighs are abducted. During this manoeuvre, a dislocated femoral head will clunk back into the acetabulum (Ortolani maneuver). This palpable clunk can be felt by the middle finger of each hand placed over each great trochanter. Both hips should be examined independently. Limitation of abduction is an early sign of congenital dislocation. Suspicion should be confirmed by an x-ray on hip regions.

c) Skin anomalies: Birth marks, naevi and pilonidal sinus.

d) Back anomalies: Meningocele and meningomyeloceles.

e) Genital anomalies: Undescended testes, hypospadius and hydrocele.

f) Hidden anomalies: Congenital heart disease, respiratory anomalies (choanal atresia, tracheoesophageal fistula), gastrointestinal (diaphragmatic hernia, intestinal obstruction) and renal anomalies (congenital hydronephrosis) are the most common.

Life-threatening congenital anomalies

Anomaly	Clinical presentation
Bilateral choanal atresia	Respiratory distress at birth (increases with feeding and decreases with crying). Failure to pass a catheter through nostrils.
Tracheoesophageal fistula	Vomiting, choking and cyanosis on feeding. Failure to pass a nosogastric tube to stomach.
Diaphragmatic hernia	Respiratory distress and mediastinal shift. Scaphoid abdomen.
Intestinal obstruction	Bile-stained vomiting, abdominal distension. In imperforate anus: Inability to pass a thermometer through the anal canal.
Meningomyelocele	Back swelling.
Congenital cyanotic heart disease	Central cyanosis with or without murmurs Chest x-ray, ECG and echocardiography are necessary.
Gastroschisis, omphalocele	Intestinal obstruction.
Renal agenesis	Anuria, renal failure.

3. Birth injuries: They include potentially avoidable mechanical injuries occurring during labor or delivery. Common injuries are:

a) Cranial injuries: Caput succedaneum is a diffuse edematous swelling of the soft tissue of the scalp over the presenting part of the head. It may extend over the middle line and may be associated with ecchymotic patches. The edema subsides spontaneously within the first dew days. *Cephalohematoma* is a subperiosteal hemorrhage that presents as a firm swelling limited to the surface of one cranial bone usually the parietal. The swelling does not appear except after several hours after birth. Anemia and jaundice are the main complications and phototherapy may be needed. It usually subsides gradually over 4-6 weeks. Associated skull fractures or even intracranial hemorrhage should be excluded. The swelling usually subsides spontaneously over 2 - 8 weeks depending on the size. Incision and drainage is contraindicated as it may lead to serious infection. *Subaponeurotic hemorrhage* between the scalp aponeurosis and subperiosteum may occasionally follow vacuum deliveries and may lead to hypovolemic shock, anemia and jaundice. Whole blood transfusion may be necessary in severe cases. *Erythema,*

abrasions and bruises are commonly seen in the face or scalp soft tissues following instrumental deliveries.

b) Intracranial injuries: Hypoxic-ischemic encephalopathy and intracranial hemorrhage are common serious injuries. Disturbed consciousness, convulsions and hypoventilation are the main clinical presentations (see neonatal convulsions).

c) Spinal cord injuries: Forceful longitudinal or lateral traction on the spine may lead to injury of the lower cervical and upper thoracic cord. Paralysis with flaccidity below the lesion occurs with accompanying constipation and urinary retention. Intercostal paralysis and hypoventilation may be associated. In survivors, initial flaccidity is replaced by rigidity after several weeks or months.

d) Peripheral nerve injuries: Injury to brachial plexus following traction on the head and neck is common and leads to paralysis of one upper limb. In *Erb's palsy* (C5, C6), the affected arm is flaccid with forearm pronated and wrist flexed (waiter's tip position). Moro reflex is asymmetric but finger movements and grasp reflex are normal. In *Klumpke palsy* (C7, C8, T1), the forearm and hand are paralyzed (absent grasp reflex). Associated ipsilateral ptosis and myosis may be associated. In *phrenic palsy* (C4, C5, C6) paralysis of one upper limb similar to Erb's palsy occurs in addition to a unilateral diaphragmatic paralysis. Cyanosis, irregular labored breathing, diminished breath sounds on the affected side and absent abdominal bulge on inspiration (paradoxical or seesaw movements) are the main findings. *Facial palsy (VII)* is usually peripheral from forceps pressure and results in absent facial or forehead movements of the affected side during crying. Failure to close the eye in the affected side is evident and it needs protection.

e) Fractures: *Fracture of clavicle* is the most common. The main signs are inability to move the affected limb and absent Moro reflex on the affected side. Crepitus and bony irregularity may be palpated. Callus formation appears within a week and produces visible swelling. The condition should be differentiated from other causes of inability to move one upper limb and asymmetric Moro reflex especially Erb's palsy and fracture of humerus.

f) Visceral injuries: *Liver injury* and formation of subcapsular hematoma may occasionally occur and lead to anemia, jaundice and respiratory distress. The abdomen may appear blue and right upper quadrant mass may be palpated. *Splenic injury* may also occur alone or in association with liver injury.

1. Low Birth weight Baby

Prematurity	Intrauterine growth retardation (IUGR)
Premature baby (50%)	**Dysmature baby (45%)**
Idiopathic	Maternal chronic illness
Antepartum hemorrhage	Toxemia of pregnancy
Premature rupture of membranes	Multiple pregnancy
Cervical incompetence	
Meternal chronic illness	**Hypoplastic baby (5%)**
Maternal infections	Chromosomal disorders
Maternal age below 16 or above 35	Congenital infections
Multiple pregnancy	Congenital anomalies
Polyhydramnios	
Fetal anomalies	

Both prematurity and intrauterine growth retardation may coexist

Low birth weight (weight of 2500 gm or less) is a common condition occurring in about 8% of all births. The incidence is higher in low socio-economic classes where maternal illnesses and nutritional deficiencies are commoner.

- **Premature baby** is a baby born before 37 weeks of gestations. It accounts for 50% of cases of low birth weight. The degree of prematurity and birth weight depends on the gestational age.
- **Dysmature baby (asymmetric IUGR)** is a full term baby who appears small for his gestational age. It accounts for about 45% of cases of low birth weight. The main cause of retardation is *fetal malnutrition* due to placental insufficiency. The baby has an *asymmetric retardation* and the head is relatively larger.
- **Hypoplastic baby (symmetric IUGR)** is a low birth weight baby that accounts for about 5% of all cases. The cause of retardation is a *serious fetal problem* mainly chromosomal abnormalities (trisomies and deletions) and congenital infections. The baby has a *symmetric retardation* because brain growth is also impaired (i.e., the head is not relatively larger). This type is obviously more serious than asymmetric retardation.

Comparison between low birth weight babies

	Premature baby	Dysmature baby	Hypoplastic baby
Incidence	50%	45%	5%
Causes	Mainly maternal	Fetal malnutrition	Serious fetal problem
Features of prematurity	Present	Absent	Absent
Head size	Proportionate	Relatively larger	Proportionate
Postnatal growth	Slow	Rapid	Failure to thrive

- What is the degree of low birth weight?
- Is it prematurity, intrauterine growth retardation or both?
- What is the estimated gestational age?
- What are the complications?

1. What is the degree of low birth weight?

As the mortality rate is largely dependent on birth weight and gestational age, low birth weight is classified into the following 4 grades:

1. Low birth weight (LBW): It is a weight between 2500 - 1500 gm. The cause is either mild prematurity or intrauterine growth retardation. The mortality rate is very low in this group (not more than 5%).

2. Very low birth weight (VLBW): It is a weight between 1500 - 1000 gm. The main cause is moderate prematurity. The mortality rate is significantly higher in this group (more than 20%).

3. Extremely low birth weight (ELBW): It is a weight between 1000 - 750 gm. It is mainly caused by severe prematurity. The mortality rate is very high in this group (more than 40%).

4. Impossibly or incredibly low birth weight (ILBW): It is a weight below 750 gm. It is caused by extreme prematurity, and the infant is actually "immature". The mortality rate in this group is probably exceeding 80%.

2. Is it prematurity, intrauterine growth retardation or both?

Clinical differentiation between prematurity and intrauterine growth retardation depends on the activity, skin, muscle tone and characteristic physical features:

1. Premature baby: The main diagnostic features are:

a) ***Activity:*** It is proportionate to the gestational age but it is proportionately less when compared to dysmature baby of the same birth weight. Most prematures with very low birth weight (below 1500 gm) have a poor suckling power.

b) ***Skin:*** The skin of premature baby is reddish in color and has a waxy appearance. It is covered with a fine hair (lanugo). The umbilical cord is normal.

c) ***Muscle tone:*** Premature baby has a posture of incomplete flexion of the limbs. Frog-leg position and head lag may be evident in severe cases.

d) ***Features of prematurity:*** The premature baby has incomplete sole creases, under-developed genitalia (undescended testes and small scrotum in males and prominent labia minora in females), small breast nodule (less than 3 mm), underdeveloped ear lobule (shapeless and pliable) and fine woolly scalp hair.

2. Dysmature baby (asymmetric IUGR): The head is relatively larger and:

a) Activity: He is generally active and he may be even hyperalert, opening his eyes and looking around with a wizened old man look. He has a good suckling power.

b) Skin: The skin of dysmature baby is pale in color. It looks loose and dry with cracking and peeling. The cord is pencil-like and dries rapidly. In severe cases, marked loss of subcutaneous fat and muscle wasting may occur.

c) Muscle tone: Dysmature baby has a posture of complete flexion of the limbs.

d) Features of maturity: It pure cases of dysmaturity, the physical features of prematurity are absent. Sole creases are complete with deep indentations, genitalia are developed, breast nodule is 5 mm, ear lobule is cartilaginous and scalp hair is coarse and silky.

3. Hypoplastic baby (symmetric IUGR): The main difference from dysmature baby is that the head is not relatively larger (symmetric retardation). Other clinical features suggesting chromosomal abnormalities (abnormal features, congenital heart disease) or congenital infection (jaundice, hepatomegaly) may be present. The postnatal growth is slow and failure to thrive in infancy is common.

3. *What is the estimated gestational age?*

Gestational age can be estimated postnatally by different ways:

1. Obstetric calculation: Gestational age can be calculated from the date of birth and the date of the first day of last menstrual period. This method is inaccurate due to the frequent occurrence of irregular menses.

2. Accurate assessment: It is recently made by the ***"expanded new Ballard score"***. The score uses 13 criteria (7 external physical and 6 neurological). The score is refined to include extremely premature infants (see text). The score has replaced the old complicated "Dubowitz score" using 21 criteria.

3. Simple rough assessment: Practical and rapid assessment can be made depending on the birth weight and time of appearance of some reflexes. This method is useful in pure prematurity not associated with intrauterine growth retardation.

Gestational age	Birth weight	Time of appearance of reflexes
28 weeks	1000 gm	Pupillary reaction to light
30 weeks	1250 gm	Head turn in prone position
32 weeks	1500 gm	Glabellar reflex
34 weeks	2000 gm	Grasp reflex
36 weeks	2500 gm	Grasp reflex (you can lift the baby up)

4. What are the complications?

Several complications are commonly seen especially in prematures with very low and extremely low birth weight. The main complications are:

1. Neurological complications: Prematures are at a risk of *hypoxic-ischemic encephalopathy* and *intracranial hemorrhage*. Disturbed consciousness, convulsions and increased intracranial pressure (bulging fontanel) are the main findings.

2. Respiratory complications: *Hyaline membrane disease* due to surfactant deficiency is the most common. The incidence and severity of illness is more in those with a shorter gestational age. *Recurrent apnea* is also common in those with gestational age less than 32 weeks. *Bronchopulmonary dysplasia* is a common complication in those exposed to high oxygen pressure and prolonged mechanical ventilation and it leads to a prolonged respiratory distress. Other complications as pneumothorax, pulmonary hypoplasia and pulmonary hemorrhage may also occur.

3. Metabolic complications: *Hypothermia* is a common serious complication of low birth weight babies. *Hypoglycemia and hypocalcemia* are also common and may lead to convulsions. *Exaggerated physiological jaundice* is a definite risk as kernicterus commonly occurs at a lower bilirubin levels (below 20 mg/dl).

4. Infections: Premature babies are immunologically deficient and are susceptible to serious fatal infections. Septicemia, pneumonia and meningitis are the most common. The invading organisms are bacterial, viral, fungal or protozoal (see neonatal infections).

5. Nutritional and gastrointestinal complications: *Poor suckling* is a common feeding problem of very low birth weight babies that usually necessitates nasogastric tube feeding. *Gastrointestinal intolerance* (as vomiting and abdominal distension) is also common and may require the use of diluted formulas, special low birth weight formulas or expressed mother's milk. *Necrotizing enterocolitis* is a common serious problem of very low birth weight infants that leads to vomiting, abdominal distension, bleeding per rectum and may be intestinal perforation and peritonitis (see neonatal vomiting).

6. Ophthalmologic complications: Oxygen toxicity to the developing retina may lead to *retrolental fibroplasia* and blindness. Oxygen should be only given in concentrations that relieves hypoxemia and keeps PaO_2 between 60 - 70 mmHg.

7. Cutaneous complications: *Pitting edema* over the hands, feet and legs is a common benign and transient finding of severe prematurity. *Sclerema*, on the other hand, is a serious fatal complication of severe prematurity especially those exposed to prolonged hypothermia. Other predisposing factors are hypoxia, acidosis and septicemia. It starts as a skin hardening over lower limbs and abdominal wall. It may rapidly extend to involve the chest wall leading to hypoventilation and death.

8. Congenital anomalies: The incidence of congenital anomalies is higher in low birth weight infants. Chromosomal disorders and congenital heart diseases are the most common.

2. Neonatal Convulsions

Brain damaged convulsions	Metabolic convulsions
Hypoxic ischemic encephalopathy	Hypoglycemia (below 30 mg/dl)
Intracranial hemorrhage	Hypocalcemia (below 6 mg/dl)
Neonatal meningitis	Hypomagnesemia (below 1.5 mg/dl)
Kernicterus	Hyponatremia (below 120 mEq/liter)
Cerebral anomalies	Hypernatremia (above 150 mEq/liter)
	Other cause (uncommon)
	Errors of metabolism
	Drugs
	Toxins

Both conditions may coexist in the same patient
The cause may remain unknown in up to 8% of cases

Convulsions in the newborn is a common potentially serious problem that occurs in about 2% of full-terms and in up to 10% of very low birth weight babies.

Hypoxic-ischemic encephalopathy is by far the commonest cause (50% of cases), followed by intracranial hemorrhage (20%) and neonatal meningitis (10%). Common metabolic causes as hypoglycemia and hypocalcemia occur in about 10% of cases. Most cases of convulsions occur during the first week after birth and particularly during the first few days.

- What are the characters of convulsions?
- Is it brain damaged or metabolic convulsions?
- What is the cause?

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1. *What are the characters of Convulsions?*

Description of convulsions should include the following aspects:

1. Type of convulsions: Neonatal convulsions can be classified into 5 types:

a) Subtle: It is the commonest type (50% of cases). It may include oral movements (sucking, chewing or yawning), eye movements (repetitive blinking, nystagmus or tonic horizontal deviation), limb movements (bicycling or pedaling) or respiratory movements (irregular breathing or apnea). Apnea due to subtle fits is usually associated with tachycardia or normal heart rate while apnea due to other causes is usually associated with bradycardia.

b) Focal clonic: It is a rhythmic twitching of muscle groups especially in the face and extremities with focal distribution.

c) Multi-focal clonic: Several muscle groups are involved simultaneously.

d) Tonic: It is a rigid posturing of extremities and trunk (decorticate or decerebrate), which may be focal or generalized and may be associated with clonic movements or apnea.

e) Myoclonic: It is a brief focal or generalized jerks of extremities or body mainly in the distal muscle groups.

Tonic and myoclonic fits have a poor prognosis as they reflect a diffuse CNS disease or intraventricular hemorrhage. Subtle and clonic fits have a better prognosis.

Convulsions should not be confused with jitteriness, which is commonly seen in normal newborns or in association with hypoglycemia, hypocalcemia, hypoxia or in infants of diabetic mothers. *Jitteriness* is a tremor-like movements that is usually precipitated by sensory stimuli and can be stopped by holding the infant's extremity. It is not associated with abnormal eye movements or EEG abnormalities.

2. Onset of convulsions: Convulsions occurring immediately after birth may be due to dilutional hyponatremia or drug-withdrawal. Convulsions during the first day are mostly due to hypoxic-ischemic encephalopathy or metabolic causes as hypoglycemia or hypocalcemia. In intracranial hemorrhage, the onset of convulsions is usually after the first day and in meningitis, it is usually not during the first few days. Convulsions that appear after 3 - 4 days in an infant who was normal at birth and was fed normally before the onset of convulsions should suggest errors of metabolism. After the first week, convulsions is mostly due to meningitis or late-onset hypocalcemia.

3. Duration and frequency of convulsions: Fits may be very transient (lasting for seconds), transient (lasting for few minutes), short (lasting for 5 -15 minutes) or prolonged (more than 15 minutes). Fits may be also infrequent (just few fits), frequent (recurring several times per day) or very frequent (recurring every hour or less). Prolonged and very frequent fits have a poor prognosis.

4. Response to therapy: Fits can be easily controllable, difficult to control or intractable (not responding to combined anticonvulsant therapy). The prognosis of intractable fits and fits persisting for more than 3 days is generally poor.

2. Is it brain damaged or metabolic convulsions?

Clinical differentiation depends on 4 clinical criteria; type of convulsions, associated neurological findings, general condition and respiratory pattern.

1. In brain damaged convulsions, convulsions are usually tonic and may be clonic also. Other neurologic signs are usually present as disturbed consciousness (lethargy or coma), increased intracranial pressure (bulging fontanel), lateralizing signs (unequal pupils or focal motor weakness) or meningeal irritation (neck retraction and/or arched back). The baby looks sick with poor activity, weak or absent suckling and vomiting. In advanced cases, there is respiratory depression with slow irregular respiration and apneic spells.

2. In metabolic convulsions, convulsions are usually clonic and the baby does not look sick except in hypoglycemia and errors of metabolism. There are no other neurological findings and no respiratory depression.

3. Both conditions (brain damaged and metabolic) may coexist in the same patient. Hypoglycemia and/or hypocalcemia are commonly present in patients with hypoxic-ischemic encephalopathy and intracranial hemorrhage.

3. What is the cause?

Although the cause can be suggested in many cases, some investigations are required to confirm the diagnosis.

Possible investigations of neonatal convulsions

Blood sugar, calcium, magnesium and sodium: In ALL cases.
Cranial ultrasonography or CT scan: In brain damaged convulsions.
Lumbar puncture and CSF examination: In suspected meningitis.
Sepsis screen (CBC, ESR, CRP, blood culture): In suspected septicemia or meningitis.
Metabolic screen (acid-base balance, ammonia level, aminogram): In suspected errors of metabolism or in unexplained convulsions.

A) BRAIN DAMAGED CONVULSIONS

1. Hypoxic-ischemic encephalopathy: It is by far the commonest cause (50% of cases). It occurs in infants exposed to perinatal hypoxia, which results in brain edema and encephalopathy. The patient usually presents with low Apgar score and cyanosis at birth. Convulsions usually start within 12 hours after birth and usually last for few days. Other neurological findings and respiratory depression are present with variable degrees according to the severity and the duration of hypoxia. Other manifestations of hypoxia may be also present (see below). Prognosis is generally good in mild to moderate cases. In severe cases characterized by prolonged fits and coma, death or severe neurological sequelae (epilepsy, motor and intellectual deficits) may occur. Cranial ultrasonography or CT scan is important to demonstrate brain edema and to exclude intracranial hemorrhage.

Clinical staging of hypoxic-ischemic encephalopathy

Sign	Mild (stage 1)	Moderate (stage 2)	Severe (stage 3)
Convulsions	No	Short fits	Prolonged fits
Consciousness	Hyperalert	Lethargy	Coma
Muscle tone	Normal	Hypotonia	Flaccidity
Suckling	Weak	Poor	Absent

Multiple organ system effects of hypoxia

System	Effects
Neurologic	Hypoxic-ischemic encephalopathy, intracranial hemorrhage.
Cardiovascular	Myocardial ischemia, cardiogenic shock.
Respiratory	Pulmonary hypertension, pulmonary hemorrhage.
Metabolic	Acute renal Failure (acute tubular or cortical necrosis). Hypoglycemia, hypocalcemia, hyponatremia.
Hematologic	Disseminated intravascular coagulation (DIC).
Digestive	Perforation, ulceration, hemorrhage.

2. Intracranial hemorrhage: It is the second most common cause of neonatal convulsions (20% of cases). It occurs principally in 3 groups of patients: (1) those with severe prematurity, (2) severe perinatal hypoxia and (3) severe birth trauma to the head. Occasionally, bleeding may follow disseminated intravascular coagulation or congenital vascular anomalies. Bleeding may occur in one or more of the following 5 sites (epidural, subdural, subarachnoid, intracerebral and intraventricular). Intraventricular hemorrhage (IVH) is the most serious and most common site especially in prematures and in those with severe hypoxia. In addition to the clinical findings of hypoxic-ischemic encephalopathy, intracranial hemorrhage should be considered in the following clinical situations: (1) onset of signs in the second or third day, (2) persistence of convulsions and other neurological signs for more than a few days, (3) presence of lateralizing signs as unequal pupils and focal paralysis, (4) progressive pallor and fall in hemoglobin level. Cranial ultrasonography or CT scan is important for diagnosis, localization and grading of severity. Prognosis is generally poor and it depends on the site and extent of hemorrhage. Mortality rate is high and neurological sequelae (epilepsy, motor and intellectual deficits) are very common in survivors.

3. Neonatal meningitis: It is the third most common cause of neonatal convulsions (10% of cases). It occurs at any time during the neonatal period but usually not during the first few days. It may accompany cases of neonatal septicemia especially those of late-onset sepsis. It may also follow infected wounds or infected meningomyelocele. Clinical manifestations start with nonspecific features as poor suckling, vomiting, irritability and fever or hypothermia. The classic signs appear late and include convulsions, disturbed consciousness and increased intracranial pressure (bulging fontanel). Lumbar puncture and CSF examination is important for diagnosis. Other laboratory means for diagnosis of sepsis as CBC, ESR and CRP are also important. Prognosis depends on the time of diagnosis and efficacy of antibiotic therapy.

4. Kernicterus: It occurs as a complication of severe neonatal hyperbilirubinemia when indirect serum bilirubin exceeds the critical level (20 mg/dl in full-terms and lower values in low birth weight babies). Untreated Rh disease is the commonest cause. Clinical manifestations usually appear between 3 -6 days after birth. In addition to deep

jaundice, the baby looks very sick with poor suckling, vomiting and absent Moro reflex. Twitches and convulsions then follow with characteristic spasms and rigidity (opisthotonos). Mortality rate is very high (75%) and the remainders develop cerebral palsy in late infancy and early childhood (hypotonia, choreoathetosis).

5. Cerebral anomalies: Rare anomalies as lissencephaly, schizencephaly, holoprocencephaly or adrenoleukodystrophy may be the cause. A neurocutaneous syndrome as tuberus sclerosis may cause intractable convulsions. CT scan of the head or magnetic resonance imaging (MRI) is essential for diagnosis of various anomalies.

B) METABOLIC CONVULSIONS

1. Hypoglycemia: It occurs mainly in low birth weight babies, infants of diabetic mothers, infants of toxemic mothers and in sick neonates (hypothermia, hypoxia or sepsis). Persistent or recurrent hypoglycemia should suggest errors of metabolism as galactosemia, glycogen storage disease or maple syrup urine disease. Clinical manifestations usually appear during the first few days and include jitteriness, convulsions and disturbed consciousness. Episodes of central cyanosis, apneic spells and heart failure may be so evident to a degree suggesting congenital cyanotic heart disease. Unlike other common metabolic causes, the baby looks sick with poor activity and weak or absent suckling. Diagnosis is confirmed by the presence of low blood sugar level (below 30 mg/dl) and disappearance of symptoms with I.V. glucose administration (2 - 4 ml/kg of glucose 10%).

2. Hypocalcemia: It may appear early (in the first few days) or late (after the first week). ***Early hypocalcemia*** occurs mainly in premature babies, infants of diabetic mothers and in association with severe perinatal hypoxia. ***Late hypocalcemia*** occurs in some infants receiving cow milk due to the high phosphate content. The baby looks generally well in spite of the muscular twitches, jitteriness and convulsions. Diagnosis is confirmed by the presence of low serum calcium level (below 6 mg/dl). Failure of response to I.V. calcium gluconate should suggest an associated condition as hypoxic-ischemic encephalopathy or hypomagnesemia.

3. Hypomagnesemia: It is less common than hypoglycemia and hypocalcemia. It occurs mainly in low birth weight babies, infants of diabetic mothers and in those receiving intravenous fluids without supplementation of magnesium. It should be also suspected in every case of convulsions with normal glucose and calcium level or in case of tetany not responding to I.V calcium. Diagnosis is confirmed by low serum magnesium level (below 1.5 mg/dl). It responds to I.V. magnesium (1.0 ml/kg of magnesium sulphate 10%). Primary hypomagnesemia is a rare condition characterized by defective intestinal absorption of magnesium. Tetanic spasms starting in neonatal period or early infancy and not responding to I.V. calcium is the main presentation.

4. Dilutional hyponatremia: It occurs in infants born to mothers who received a large amount of intravenous hypotonic solutions shortly before birth. It may also occur in infants with renal salt losses, or those receiving hypotonic I.V. fluids. Diagnosis is confirmed by low serum sodium level (below 120 mEq/liter). It responds to I.V. sodium chloride solution 3%.

5. Hypernatremia: It may occur with dehydration or iatrogenic due to repeated bicarbonate therapy or hypertonic solutions. Diagnosis is confirmed by a high serum sodium level (above 150 mEq/liter).

6. Errors of metabolism: Although uncommon, errors of metabolism should be considered in any infant who is normal at birth and becomes symptomatic after a few days of milk intake. Symptoms include poor feeding, vomiting, lethargy and convulsions. The condition may progress rapidly to deep coma. Three main categories of aminoacid disorders should be considered: (1) ***aminoacidopathies*** as maple syrup urine disease, phenylketonuria and nonketotic hyperglycemia, (2) ***organic acidemia***, as propionic acidemia and methylmalonic acidemia, (3) ***urea cycle disorders*** with hyperammonemia as argininemia, citrullinemia and argininosuccinic acidemia. Laboratory approach for diagnosis should initially include plasma ammonia level and acid-base status:

- Hyperammonemia, without acidosis suggests *urea cycle disorders.*
- Metabolic acidosis (with or without hyperammonemia) suggests *organic acidemia.*
- Normal ammonia and pH suggests *aminoacidopathies.*

(Aminogram is necessary for precise diagnosis).

7. Drugs: Withdrawal convulsions may occur in infants born to mothers receiving large doses of sedatives or hypnotics. Clinical manifestations also include tremors, poor feeding, yawning and sneezing. Convulsions may also occur with some drugs given to the baby especially theophylline.

8. Toxins: Convulsions may occur with any severe infection especially ***septicemia***. Other manifestations suggesting sepsis are usually evident. ***Tetanus neonatorum*** occurs due to infection with clostridium tetani organism usually at birth during cutting the cord under poor hygienic conditions. The infection remains localized at the umbilicus producing powerful exotoxins, which are absorbed through motor end plates or lymphatics and produce the characteristic picture. Clinical manifestations appear after an incubation period of about one week and start with *trismus (lock jaw) and difficult milk intake. Clonic convulsions and characteristic spasms* rapidly appear with stiff extremities, neck retraction and arched back (opisthotonos). Convulsions and spasms are characterized by the following: (1) can be precipitated by the slightest stimulus (hyperexcitability), (2) intermittent early and separated by complete relaxation, (3) spasms are painful as the consciousness is not impaired, (4) may lead to intramuscular hemorrhage, fracture spine and laryngeal spasm and death. *Umbilical sepsis* is usually evident. Diagnosis is clinical and it depends on the characteristic picture. Lumbar puncture and CSF examination is normal.

C) OTHER CAUSES

Familial neonatal Convulsions is an autosomal dominant condition characterized by frequent fits in the first 3 weeks. The prognosis is excellent as the condition rarely persists beyond the neonatal period. Diagnosis depends on exclusion of other causes and the presence of positive family history.

3. Neonatal Respiratory Distress

Pulmonary causes	Extrapulmonary causes
Hyaline membrane disease	**Congestive heart failure**
Transient tachypnea of the newborn	Cyanotic CHD (as TGA, TAPVR)
Meconium aspiration syndrome	Noncyanotic CHD (as PDA, coarctation)
Neonatal pneumonia	Myocardial ischemia (shock, hypoxia)
Persistent fetal circulation	Myocarditis (viral, toxic)
Pneumothorax	Cardiomyopathy (as in IDM)
Diaphragmatic hernia	**Severe metabolic acidosis**
Congenital lobar emphysema	Severe hypoxia, shock, sepsis
Bronchopulmonary dysplasia	Acute renal failure
Other causes	Renal tubular acidosis
Bilateral choanal atresia	Errors of metabolism
Pulmonary hypoplasia	**Hematological causes**
Pulmonary atelectasis	Severe anemia (blood loss, hemolysis)
Congenital lung cysts	Polycythemia

- CHD (congenital heart disease), TGA (transposition of great arteries), TAPVR (total anomalous pulmonary venous return), PDA (patent ductus arteriosus), IDM (infant of diabetic mother).

Respiratory distress is the most common neonatal emergency and the main cause of admission to neonatal intensive care units. Hyaline membrane disease is by far the most common cause (more than 50% of cases) followed by neonatal pneumonia, transient tachypnea and meconium aspiration.

- What is the degree of distress?
- What is the cause of distress?

1. *What is the degree of distress?*

Clinical assessment of the degree of distress is important for determination of the severity and course of illness and for choice of the appropriate line of respiratory support.

Grading of respiratory distress

Grade I (mild distress): Rapid respiration (above 60/minute) and working alae nasi.
Grade II (moderate distress): Intercostal and subcostal retractions.
Grade III (severe distress): Expiratory grunting.
Grade IV (advanced distress): Central cyanosis and disturbed consciousness.

Clinical evaluation should be combined with blood gas analysis to identify those in respiratory failure (PaO_2 below 50 mmHg with or without $PaCO_2$ above 50 mmHg). Persistent hypoxemia in spite of oxygen therapy and/or CO_2 retention ($PaCO_2$ above 60 mmHg) are indications for mechanical ventilation.

Respiratory distress should not be confused with respiratory depression as both can lead to cyanosis and respiratory failure.

Neonatal respiratory failure

	Lung failure (Type I RF) (Respiratory distress)	Pump failure (Type II RF) (Respiratory depression)
Causes	Pulmonary causes Extrapulmonary causes	CNS narcosis: Drugs, anesthesia Severe brain insult Severe pulmonary disease
Clinically	Tachypnea ± retractions, grunting, cyanosis.	Slow irregular respiration with frequent apnea, cyanosis. Disturbed consciousness.
Blood gases	Lung failure (Type I RF) • Arterial hypoxemia (low PaO_2) ± hypoventilation (high $PaCO_2$)	Pump failure (Type II RF) • hypoventilation (high $PaCO_2$) ± hypoxemia (low PaO_2)
Therapy	• Oxygen therapy ± Assisted ventilation	• Assisted ventilation ± Oxygen therapy

• Acute respiratory failure is always associated with acute respiratory acidosis (low pH, high bicarbonate) or combined respiratory and metabolic acidosis (very low pH, normal bicarbonate).

2. *What is the cause of distress?*

In spite of the long list of conditions presenting with respiratory distress, it is usually not difficult to distinguish between the different causes based upon the history, clinical examination and simple investigations. Clinical evaluation should include the mode of delivery (vaginal or C.S.), birth weight, gestational age, color (pallor, plethora or cyanosis) and systemic examination (CNS, chest, heart and abdomen). Initial clinical exclusion of congestive heart failure is important. Chest examination should begin with comparison of the air entry on both sides to detect conditions with unequal air entry as pneumothorax and diaphragmatic hernia.

Possible investigations of neonatal respiratory distress

Chest x-ray: in ALL cases. To distinguish between different pulmonary causes.
Blood gases: in ALL cases. To detect metabolic acidosis and respiratory failure.
Hemoglobin level and hematocrit value: To detect anemia and polycythemia.
Sepsis screen (CBC, ESR, CRP): With suspected pneumonia.
Echocardiography: With suspected congenital heart disease.

A) PULMONARY CAUSES

1. Hyaline membrane disease: It is by far the most common cause. It occurs principally *in premature babies* due to deficient synthesis of surfactant by type II alveolar cells, which results in massive alveolar atelectasis. Other factors as cold injury, anoxia, acidosis and hypovolemia further impair surfactant synthesis. Manifestations of respiratory distress appear at birth or few hours later and increase gradually to reach its peak in the second or third day. Auscultation of the chest reveals bilateral fine consonating crepitations and air entry may be markedly diminished especially in severe cases. Chest x-ray reveals fine granular appearance (ground glass appearance) in mild to moderate cases and complete opacification of both lung fields (white lungs) in severe cases (see Basis Pediatric Radiology). Natural gradual improvement occurs in survivors after the third day over 3-5 days Complications as respiratory failure, apnea, intraventricular hemorrhage and paralytic ileus are common. Mechanical ventilation may be complicated with pneumothorax, interstitial emphysema and bronchopulmonary dysplasia and the course may be prolonged for few weeks.

2. Transient tachypnea of the newborn: It mainly occurs *in full term babies* born by Caesarean section due to delayed clearing of lung fluids. Respiratory distress appears within few hours after birth and is usually mild (just tachypnea). Rapid improvement occurs over 24 hours but tachypnea may remain for 2 - 3 days. Chest x-ray reveals coarse streaking and fluid in the fissures (wet lung appearance).

3. Meconium aspiration syndrome: It mainly occurs *in full term and post-term babies* subjected to fetal distress with passage of meconium into the amniotic fluid. Aspiration of meconium-stained amniotic fluid usually occurs at birth and results in respiratory distress within few hours after birth. The skin and umbilical cord may be stained with meconium. Pneumothorax and pneumonia are common complications of severe cases. Chest x-ray reveals hyperinflated lungs with bilateral patchy consolidation. ***Similar disorders*** may be caused by aspiration of normal amniotic fluid or milk and result in aspiration pneumonia. Predisposing conditions, as tracheoesophageal fistula and gastroesophageal reflux should be considered.

4. Neonatal pneumonia: It can be congenital or acquired. ***Congenital pneumonia*** is characterized by early onset of respiratory distress within 3 - 6 hours after birth (early onset pneumonia). The clinical and radiological findings may be very similar to those of hyaline membrane disease or aspiration pneumonia. Helpful differentiating features include temperature instability, apneic spells and acidosis. Skin rash or hepatosplenomegaly may be also present. In ***acquired pneumonia,*** the onset of respiratory distress is usually after the first 24 hours or at any time in neonatal period (late onset pneumonia). It commonly follows aspiration, mechanical ventilation or septicemia. The pneumonia may be a bronchopneumonia or lobar pneumonia with massive unilateral consolidation. In case of bronchopneumonia, bilateral fine consonating crepitations is the main finding. With massive consolidation, unilateral dullness and diminished air entry over the involved area are evident. Simple sepsis

screen (CBC, ESR, CRP) is useful in suggesting an infection. Definite diagnosis depends on isolation of the organism by blood culture and culture of tracheal aspirate.

5. Persistent fetal circulation (PFC): Persistent pulmonary hypertension causes right-to-left shunting through the foramen ovale and ductus arteriosus, which results in severe hypoxemia. It may occur as an idiopathic disorder or secondary to other critical illness as hyaline membrane disease, meconium aspiration, neonatal pneumonia, diaphragmatic hernia or polycythemia. ***Idiopathic cases*** are characterized by central cyanosis unresponsive to oxygen therapy and the condition can be easily confused with congenital cyanotic heart disease. Respiratory distress is variable, chest auscultation is unrevealing and cyanosis characteristically becomes more intense with crying. In ***secondary cases***, the manifestations of the primary disease are evident in addition to central cyanosis, which becomes more intense with crying. Diagnosis depends on the presence of arterial oxygen gradient above 20 mmHg between preductal sample (right radial artery) and postductal sample (umbilical artery). Doppler echocardiography can demonstrate the shunt and measure the elevated pulmonary blood pressure.

6. Pneumothorax: It may occur ***spontaneously*** during the course of illness of a severe pulmonary disease as hyaline membrane disease, meconium aspiration, diaphragmatic hernia or congenital lobar emphysema. More commonly, it is ***iatrogenic*** and follows vigorous resuscitative measures or mechanical ventilation. Clinically, sudden deterioration of the condition with cyanosis, pallor or skin mottling should raise the possibility. Chest examination reveals diminished air entry over the involved side with mediastinal shift to the other side. Transillumination of the thorax is often helpful in emergency situations. Urgent chest x-ray is diagnostic and it reveals hypertransradiant hemithorax with absent bronchovascular markings.

7. Diaphragmatic hernia: Herniation of abdominal viscera into the thoracic cavity (mostly on the left side through the foramen of Bochdalek) may result in severe respiratory distress at birth or later in neonatal period or infancy. Chest auscultation reveals diminished air entry over the involved side with mediastinal shift to the other side. Respiratory distress in conjunction with scaphoid abdomen should always raise the possibility. Chest x-ray is usually diagnostic where multiple cysts (air-filled bowel) occupying one hemithorax and pushing the mediastinum to the other side are demonstrated (see Basic Pediatric Radiology). Pneumothorax is a common complication. It is important to know that trials of resuscitation with bag and mask may result in worsening of the condition because of the more distention of the herniated viscera.

8. Congenital lobar emphysema: It is caused by partial obstruction of a bronchus by external (cyst or aberrant vessel) or internal (plugs, mucosal folds or stenosis) conditions. The left upper lobe is the most commonly involved (50% of cases), followed by the right middle lobe (30%) and right upper lobe (20%). Half the cases are symptomatic in neonatal period but usually not during the first week. Clinical diagnosis is difficult but chest x-ray demonstrates the emphysematous lobe with mediastinal shift to the other side. Bronchoscopy is helpful in demonstrating the obstructed bronchus and in removing mucous plugs. Treatment is surgical.

9. Bronchopulmonary dysplasia (BPD): It is a chronic lung disease of progressive alveolar collapse that occurs principally in premature babies treated with mechanical ventilation for severe hyaline membrane disease. Clinically, instead of the natural improvement on the 3rd or 4th day, the condition deteriorates and respiratory distress persists for few or several weeks and the baby becomes ventilator and oxygen dependent. Chest auscultation may reveal fine crepitations and expiratory wheezing. Cor-pulmonale and congestive heart failure commonly occur. Radiological findings are gradually changing over weeks.

Radiological stages of bronchopulmonary dysplasia

Stage I (first week): Ground glass appearance similar to hyaline membrane disease.
Stage II (second week): Generalized opacity and pulmonary plethora.
Stage III (third week): Bilateral multiple small cysts (bubbly lungs).
Stage IV (fourth week): Hyperinflation, widespread stranding, cardiomegaly.

Bronchopulmonary dysplasia should be differentiated from other causes of neonatal chronic lung disease characterized by chronic respiratory distress.

Causes of neonatal chronic lung disease

Bronchopulmonary dysplasia: Mainly in ventilated prematures.
Wilson-Mikity syndrome: Mainly in nonventilated very low birth weight babies.
Chronic pulmonary insufficiency of prematurity.
Chronic pneumonia: Chronic bacterial or viral interstitial pneumonia.
Recurrent aspiration: With tracheoesophageal fistula, gastroesophageal reflux.
Congenital lobar emphysema.
Heart failure due to patent ductus arteriosus.

10. Other causes: Several other conditions may lead to respiratory distress in the newborn. ***Bilateral choanal atresia*** leads to marked distress and cyanosis, which is relieved by crying. Diagnosis is confirmed by failure to pass a nasogastric tube through both nostrils. ***Pulmonary hypoplasia*** occurs in association with lung compression as diaphragmatic hernia or with oligohydramnios. ***Pulmonary atelectasis*** occurs in extreme prematurity (less than 28 weeks). ***Massive pulmonary hemorrhage*** is a form of hemorrhagic pulmonary edema that complicates cases of severe hypoxia, hypothermia, hypoglycemia, pneumonia and coagulation defect as DIC. The onset is usually between the second and fourth day after birth where a red frothy fluid is aspirated from the mouth or from the endotracheal tube in ventilated babies. Chest auscultation reveals widespread crepitations. ***Cystic adenomatoid malformation*** is a form of congenital cystic disease of the lung. The multiple cysts may be large, medium-sized or small. The condition should be differentiated from *other causes of* ***multiple cysts*** especially diaphragmatic hernia, bronchopulmonary dysplasia and multiple pneumatoceles of staphylococcal pneumonia. Other lung cysts as bronchogenic cyst and sequestration of the lung are very rare.

B) EXTRAPULMONARY CAUSES

1. Congestive heart failure: Clinical diagnosis of congestive heart failure depends on the presence of the cardinal triad of 3 T (tachycardia, tachypnea and tender liver). Diagnosis of the cause can be made by clinical evaluation and echocardiography. Presence of central cyanosis and/or significant murmur suggests a congenital heart disease. Hypoxia or shock indicates a myocardial ischemia while manifestations of sepsis indicates a myocarditis.

Cardinal clinical triad of congestive heart failure

Tachycardia: Heart rate above 180/minute.
Tachypnea: Respiratory rate above 60/minute.
Tender liver: The liver is enlarged and tender.

2. Metabolic acidosis: Clinical diagnosis of metabolic acidosis depends on the presence of deep rapid respiration (acidotic breathing). In more severe cases, disturbed consciousness becomes evident. Clinical suspicion should be confirmed by blood gas analysis where all parameters are low (pH, bicarbonate and $PaCO_2$). The severity of acidosis can be determined by the degree of lowering of pH and serum bicarbonate level.

Normal blood gases in newborn

Parameter	Value
pH	7.35 - 7.4
Bicarbonate	20 - 24 mEq/liter
$Pa\ CO_2$	35 - 40 mmHg
$Pa\ O_2$	60 - 80 mmHg

Grades of metabolic acidosis

Grade	pH	Bicarbonate
Mild	Below 7.3	Below 16 mEq/liter
Moderate	Below 7.2	Below 13 mEq/liter
Severe	Below 7.1	Below 10 mEq/liter
Profound	Below 7.0	Below 7 mEq/liter

- For assessment of acid-base status, venous samples are satisfactory.

The cause of acidosis can be identified by the clinical evaluation (hypoxia, sepsis, shock), evaluation of renal function (renal failure), aminogram (errors of metabolism) and calculation of the *anion gap* (normal in renal tubular acidosis and high in other causes of metabolic acidosis).

Anion gap = Serum sodium — (serum chloride + serum bicarbonate) = 5 - 15 mEq/liter.

3. Severe anemia or polycythemia: Measurement of hemoglobin level and hematocrit value should be a routine in every case of neonatal respiratory distress. ***Severe acute anemia*** (hemoglobin below 8 gm/dl) may result from severe hemolysis or severe blood loss. ***Polycythemia*** (hematocrit over 65%) may result from delayed cord clamping, maternofetal transfusion or placental insufficiency secondary to intrauterine hypoxia. The most common clinical manifestations of polycythemia are plethora, cyanosis, respiratory distress, lethargy, jaundice and poor suckling.

'It is more blessed to give than to receive.

4. Neonatal Jaundice

Early onset jaundice	Late onset and persistent jaundice
Acute hemolysis - Rh incompatibility - ABO incompatibility - G6PD deficiency - Large cephalohematoma Physiological jaundice Neonatal septicemia Polycythemia In this group, hyperbilirubinemia is mainly of the unconjugated type and kernicterus is the main risk.	**Unconjugated hyperbilirubinemia** Prolonged physiological jaundice Breast milk jaundice Chronic hemolytic anemia Criglar Najjar syndrome, Gilbert disease **Conjugated hyperbilirubinemia** Inspissated bile syndrome Neonatal hepatitis Extrahepatic biliary atresia Intrahepatic biliary atresia Metabolic liver disease Total parenetral nutrition Familial recurrent jaundice

Jaundice in the newborn is a very common problem, which can be physiological or pathological. It is clinically useful to classify cases into two groups as the causes; clinical evaluation and investigations are different in both groups. In ***early onset jaundice***, jaundice appears during the first week and usually subsides over one or two weeks. In ***late onset and persistent jaundice***, jaundice either appears after the first week or persists for more than 2 -3 weeks.

A) EARLY ONSET JAUNDICE

In this group, the main 3 causes are acute hemolysis, physiological jaundice and septicemia. Clinical differentiation between these conditions depends on:

- Onset and severity of jaundice.
- Presence or absence of anemia.
- General condition (activity and suckling power).
- Presence or absence of complications especially bilirubin toxicity (kernicterus).

Some laboratory investigations are also necessary for accurate diagnosis.

Possible investigations of early onset jaundice

- Serum bilirubin level (total, unconjugated, conjugated): In ALL cases.
- Hemoglobin level, Coombs test, red cell morphology, reticulocytic count: In suspected hemolysis.
- G6PD enzyme activity: In hemolysis not due to Rh or ABO incompatibility.
- Sepsis screen (CBC, ESR, CRP, blood culture): In suspected septicemia.

1. Acute hemolysis: In this condition, jaundice appears at birth or during the *first day* and it is commonly severe. Serum bilirubin level may rise rapidly to reach serious levels where kernicterus may occur. *Anemia* is evident clinically and hemoglobin level may reach below 6 gm/dl. The *general condition* is commonly affected especially with serious bilirubin levels. *Kernicterus* (see neonatal convulsions) is a real risk and it may occur when serum bilirubin exceeds the critical level, which depends on the birth weight and the condition of the baby. The critical level is lower in those with low birth weight and in sick neonates.

Critical indirect bilirubin level at which kernicterus may occur

Birth weight	Doing well baby	Sick baby
Above 2500 gm	20 mg/dl	18 mg/dl
2500 - 2000 gm	18 mg/dl	16 mg/dl
2000 - 1500 gm	16 mg/dl	14 mg/dl
1500 - 1250 gm	14 mg/dl	12 mg/dl
Below 1250 gm	12 mg/dl	10 mg/dl

• Manifestations of sickness include hypoxia, hypothermia, hypoglycemia, acidosis or infections.
• Some races (East Asians, Mediterraneans) are at a higher risk for developing neonatal indirect hyperbilirubinemia.

The cause of hemolysis can be identified by clinical and laboratory evaluation.

a) Rh incompatibility: It is the *commonest* cause of hemolysis. It occurs in some Rh positive babies born to Rh negative mothers. Hemolysis occurs due to placental passage of maternal antibodies active against the fetal red cells. The *first baby* is usually not affected as maternal sensitization usually occurs during delivery of the first baby. *Jaundice* and *anemia* are usually severe and the baby may be born with the picture of *hydrops fetalis* (pallor, edema and hepatosplenomegaly). *Kernicterus* is a common complication, which occurs when serum bilirubin exceeds the critical level. Diagnosis is confirmed by the presence of *positive Coombs test,* anemia (hemoglobin level below 10 gm/dl), reticulocytosis and unconjugated hyperbilirubinemia. Exchange transfusion is always necessary to keep serum bilirubin below the critical level.

b) ABO incompatibility: It is *less common* than Rh disease. The *first baby* may be affected. The disease is milder than Rh disease. *Jaundice* and *anemia* are not severe. *Hydrops fetalis* and *kernicterus* are rare. *Coombs test* may be negative. Diagnosis is confirmed by the presence of unconjugated hyperbilirubinemia and spherocytosis.

c) Glucose 6 phosphate dehydrogenase (G6PD) deficiency: This x-linked disease is occasionally the cause of severe hemolysis and neonatal hyperbilirubinemia. The condition should be suspected in any male newborn with acute hemolysis not due to Rh or ABO incompatibility. Diagnosis is confirmed by the presence of low enzyme activity below 20 unit/10^{12} RBC (normal activity is 100 - 200 unit/10^{12} RBC).

d) Large cephalohematoma: Hemolysis may occur in a large cephalohematoma and leads to jaundice. It should be excluded in every case of anemia and jaundice.

2. Physiological jaundice: It is the commonest cause of jaundice as it occurs in up to 40% of normal newborns and 70% of prematures due to transient immaturity of hepatic conjugation of bilirubin and increased production of bilirubin following breakdown of fetal red cells. Jaundice appears in *the second or third day* and is usually not severe (less than 12 mg/dl in full terms and 15 mg/dl in prematures). It usually subsides within one week of onset. *Anemia* is absent and the *general condition* is fair with good activity and suckling power. *Kernicterus* does not occur, as serum bilirubin does not reach critical levels except in premature babies where kernicterus may occur at lower levels. However, jaundice may be occasionally severe with serum bilirubin level above 15 mg/dl (exaggerated physiological jaundice). The main risk factors leading to exaggerated jaundice are male sex, race, cephalohematoma, polycythemia, breast-feeding and drugs as vitamin K_3. Physiological jaundice may be also prolonged and persists for more than 2 - 3 weeks (see below).

3. Neonatal septicemia: Jaundice in septicemia, if present, usually appears between the *fourth and seventh day* or later and is usually moderate in severity. *Anemia*, if present, is usually not severe. The most important clinical signs are the markedly affected *general condition*. The baby is not doing well with lethargy, poor suckling, vomiting, fever or hypothermia. In severe cases, *serious complications* may occur as septic shock, renal failure and DIC. With clinical suspicion, sepsis screen should be immediately made. It includes blood culture and other simple tests as complete blood count, erythrocyte sedimentation rate and C-reactive protein (CRP). Immediate hospitalization and combined parenteral antibiotic therapy are important.

Laboratory findings suggestive of neonatal septicemia

Total white cell count below 5000/mm^3 or above 30000/mm^3.
Band count above 10% or band/total neutrophil ratio above 0.2.
Toxic granulations in neutrophils.
Erythrocyte sedimentation rate (ESR) above 15 mm/first hour.
C-reactive protein (CRP) above 20 mg/liter.

- Positive 2 tests indicate infection in 90% of cases and 3 tests in 97% of cases.
- Recently, elevated serum cytokines (as Inerleukin- 6 and interleukin-8) are highly suggestive.

B) LATE ONSET AND PERSISTENT JAUNDICE

Jaundice appearing after the first week or persisting more than 2 weeks is produced by another group of causes and it may be unconjugated (indirect) or conjugated (direct). Three clinical questions are important:

1. Is it unconjugated or conjugated jaundice?

In ***unconjugated jaundjce,*** the skin color is bright yellow or orange and the stool is of normal color while in ***conjugated jaundice*** the skin is greenish yellow or muddy yellow and the stool is commonly pale or clay colored. Accurate differentiation is only made by determination of serum bilirubin level and its type.

2. What are the associated clinical manifestations?

In ***unconjugated group,*** jaundice is usually the only clinical finding. Anemia, if present, may suggest chronic hemolysis or hypothyroidism.

In ***conjugated group,*** jaundice is usually associated with hepatomegaly and pale or clay colored stool and the condition is known as **"neonatal cholestasis".** Other clinical findings may be present and can suggest the causative disease.

Possible clinical findings in neonatal cholestasis

History of severe hemolysis in the first week: Inspissated bile syndrome.
Low birth weight and/or microcephaly: Congenital infections.
Cataract: Galactosemia or congenital rubella.
Congenital heart disease: Congenital rubella or Alagille's syndrome.
Anemia, purpura: Congenital infection.
Hepatosplenomegaly: Congenital infection.
Not doing well (lethargy, poor suckling, vomiting): Neonatal septicemia.
Facial and/or skeletal anomalies: Alagille's syndrome.

3. What is the cause?

With determination of serum bilirubin level and its type, causes are classified into two groups:

(a) Unconjugated hyperbilirubinemia

1. Prolonged physiological jaundice: Persistence of physiological jaundice for more than 2 -3 weeks should suggest congenital hypothyroidism and measurement of T_4 and TSH or x-ray on knee region for determination of bone age should be made. Other conditions as constipation and pyloric stenosis are also associated with increased enterohepatic circulation and prolongation of physiological jaundice.

2. Breast milk jaundice: It occurs in some breast-fed infants due to presence of certain substances (as pregnandiol), which inhibit bilirubin conjugation. Jaundice appears in the *seventh day* and it gradually increases in severity till it reaches its peak during the third week. There are *no other clinical signs* and the jaundice may persist for several weeks. A therapeutic withdrawal of breast-feeding for 3 days results in a rapid decline of bilirubin level and on resuming breast-feeding, bilirubin level will not rise to its previous levels.

3. Chronic hemolytic anemias: Several types of chronic hemolytic anemias (congenital spherocytosis, sickle cell anemia or thalassemia) may uncommonly present in the neonatal period. Persistent anemia and reticulocytosis should suggest the diagnosis (see hematology). Identification of the causative disease requires study of red cell morphology (spherocytosis) and hemoglobin electrophoresis (sickle cell anemia and thalassemia).

4. Crigler Najjar syndrome: This inherited condition is the main cause of chronic nonhemolytic unconjugated hyperbilirubinemia. It has two types, which differ in mode of inheritance and severity. ***Type I*** is *autosomal recessive* and is caused by complete absence of glucoronyl transferase enzyme activity. Jaundice is severe (bilirubin exceeds 20 mg/dl) and kernicterus may occur. Phenobarbital is not useful and repeated exchange transfusions are necessary. ***Type II*** is *autosomal dominant* and is caused by deficient glucoronyl transferase enzyme activity. Jaundice is mild to moderate (5-15 mg/dl) and kernicterus does not occur. Phenobarbital is useful in lowering serum bilirubin level and exchange transfusion is not needed. Mild type II should not be confused with ***Gilbert's disease***, which is characterized by low grade unconjugated hyperbilirubinemia (below 5 mg/dl) with episodic exacerbations in response to infection. It is a benign condition, which is also inherited as an *autosomal dominant* disease and caused by an uptake defect of the liver cell membrane.

(b) Conjugated or mixed hyperbilirubinemia (neonatal cholestasis)

Clinical differentiation between different causes of neonatal cholestasis is impossible and a laboratory approach is always necessary to reach a precise diagnosis.

Laboratory approach of neonatal cholestasis

1. **Search for treatable conditions**
   Galactosemia: Reducing substance in urine.
   Septicemia: Sepsis screen (CBC, ESR, CRP, blood culture).
   Urinary tract infection: Urine analysis and culture.
2. **Search for congenital infections**
   Total IgM antibody: Level above 18-20 mg/dl is highly suggestive (normally below 5 mg/dl).
   TORCH screening: Specific IgM antibodies of TORCH agents (toxoplasma, rubella, cytomegalovirus and herpes simplex).
   Isolation of the organism by culture or polymerase chain reaction (PCR): In CMV, HSV.
3. **Search for other metabolic conditions**
   Tyrosinemia: Ferric chloride urine screening test. If positive: Aminogram.
   Apha one antitrypsin deficiency: Normal serum value is 150-250 mg/dl.
4. **Search for choledochal cyst**
   Abdominal ultrasound.
5. **Differentiation between idiopathic hepatitis and extrahepatic biliary atresia**
   Radionuclide scanning (Hida scan).
   Percutaneous liver biopsy.

In spite of multiplicity of the conditions causing neonatal cholestasis, most cases are caused by idiopathic hepatitis and extrahepatic biliary atresia. Early differentiation between these 2 conditions is important because in case of biliary atresia early surgical correction will prevent further hepatic injury and subsequent development of biliary cirrhosis.

1. Inspissated bile syndrome: It is a form of transient cholestasis that may follow a severe hemolytic disease (post-hemolytic cholestasis). The severe unconjugated hyperbilirubinemia in the first week is gradually replaced by conjugated or mixed hyperbilirubinemia and pale stool. The condition is benign as liver functions are normal and gradual complete recovery will occur over few or several weeks.

2. Neonatal hepatitis: In a small percentage of cases, neonatal hepatitis is caused by a ***congenital infection.*** The possibility should be considered in presence of other clinical findings as low birth weight, microcephaly, cataract or congenital heart disease. Fundus examination may reveal chorioretinitis and skull x-ray may show intracranial calcification. TORCH screening is useful for diagnosis and identification of the causative disease. In another small group of cases, hepatitis occurs as a complication of ***neonatal septicemia***. In this case, the baby is sick with lethargy, poor suckling, vomiting, fever or hypothermia. Sepsis screen is essential in every case of cholestasis to exclude septicemia. However, most cases of neonatal hepatitis are of unknown cause ***(idiopathic or giant cell hepatitis)***. It is the commonest cause of neonatal cholestasis as it accounts alone for up to 50% of cases. The condition has both sporadic and familial varieties. In *sporadic cases*, about 70% of patients will recover over several weeks or months. Prognosis of *familial cases* is worse and recovery rate is as low as 20%. Cases who will not recover will develop chronic liver cell failure and portal hypertension. Radionuclide scanning and liver biopsy are essential for accurate diagnosis and differentiation from other causes.

Diagnostic investigations of idiopathic neonatal hepatitis

Conjugated or mixed hyperbilirubinemia.
Markedly elevated serum transaminases ± prolonged prothrombin time.
Radionuclide scanning (Hida scan): Some excretion of the dye into the intestine occurs.
Liver biopsy: Hepatocellular necrosis, giant cell transformation, inflammatory infiltrate of portal tracts and bile duct proliferation.

3. Extrahepatic biliary atresia: It is the second most common cause of neonatal cholestasis. Jaundice usually appears after the first week and it gradually increases in severity. Pale stool and firm to hard liver are always present. The baby is usually a full term and he does not look sick in spite of the progressive jaundice. Early recognition is important, as early surgical correction will prevent further hepatic damage. Without surgery, biliary cirrhosis and death usually occur during infancy. Radionuclide scanning and liver biopsy are needed for accurate diagnosis.

Diagnostic investigations of extrahepatic biliary atresia

Conjugated or mixed hyperbilirubinemia: Conjugated fraction is more than 80%.
Radionuclide scanning (Hida scan): No excretion seen in bowel over 24 hours.
Liver biopsy: Wide portal tracts, distorted angulated bile ducts, periportal fibrosis and some giant cell transformation.
Laparatomy and intra-operative cholangiography may be needed in doubtful cases.

4. Intrahepatic biliary hypoplasia: Hypoplasia or paucity of interlobular bile ducts is occasionally the cause of neonatal cholestasis. The condition may occur as an isolated disease ***(nonsyndromatic intrahepatic biliary hypoplasia)*** or may be associated with cardiac, facial and skeletal anomalies ***(syndromatic intrahepatic biliary hypoplasia or Alagille's syndrome)***. As peripheral pulmonary artery stenosis is the most common cardiac anomaly, the disease is also called arteriohepatic dysplasia. Liver biopsy is essential for diagnosis and it demonstrates paucity of interlobular bile ducts with variable portal fibrosis.

5. Metabolic liver disease: It is occasionally the cause of neonatal cholestasis. ***Galactosemia*** is the most common and it should be routinely excluded. ***Tyrosinemia*** and ***alpha one antitrypsin deficiency*** may be also responsible. Rare causes include Gaucher disease, Niemann Pick disease and cystic fibrosis (see genetics).

6. Cholestasis with total parenteral nutrition: It occurs as a complication of parenteral nutrition, which may occur due to high protein or lipid load. The condition is commoner with prolonged nutrition for more than few weeks especially in the very low birth weight premature babies. Discontinuation of parenteral nutrition results in gradual recovery.

7. Familial recurrent cholestasis: Recurrent cholestasis may occur with several familial conditions. ***Dubin-Johnson syndrome*** is characterized by recurrent cholestasis and dark brown pigment in liver cells. ***Rotor syndrome*** is also characterized by recurrent cholestasis but without a pigment in liver cells. ***Benign recurrent cholestasis*** is characterized by complete remission between the recurrent episodes of cholestasis. Unlike the above 2 syndromes, the condition is benign and the liver function is not impaired.

5. Neonatal Sepsis or Septicemia

Early onset sepsis	Late onset and nosocomial sepsis
Main causative organisms	**Main causative organisms**
Group B streptococcus	Staphylococcus aureus, S. epidermidis
Escherichia coli	Pseudomonas aerugenosa
Listeria monocytogenes	Klebsiella
Hemophilus influenza	Viral (herpes simplex, cytomegalovirus)
Klebsiella	Candida albicans
Streptococcal pneumoniae	Other organisms as early onset sepsis
Main risk factors	**Main risk factors**
Premature rupture of membranes	Hospitalization
Maternal fever or leukocytosis	Endotracheal intubation
Uterine tenderness	Mechanical ventilation
Chorioamnionitis	Umbilical catheterization, sepsis
Resuscitation with ET tubes	Total parenteral nutrition, tube feeding

Prematurity is a risk factor in both groups and it is associated with 5-10 times greater risk of sepsis

Neonatal sepsis or septicemia is a clinical syndrome resulting from a serious infection in the first month of life. It is a common serious problem with mortality rate ranging from 10 to 40%. In ***early onset disease,*** the infection is mostly acquired from the mother and clinical manifestations appear during the first three days or up to the 7th day. It is mainly caused by organisms present in the cervix or vaginal canal. In ***late onset and nasocomial disease,*** the infection is acquired postnatally from the community or the hospital and clinical manifestations appear after the first three days or the first week. It is mainly caused by other more virulent organisms at staphylococcus and pseudomonas. Nonbacterial infections with viruses (herpes simplex, cytomegalovirus) and fungi (candida albicans) may be the cause of late onset sepsis.

- How to diagnose neonatal sepsis?
- How to confirm the diagnosis?

1. How to diagnose neonatal sepsis?

It should be emphasized that diagnosis of neonatal sepsis is a *clinical diagnosis*, which can be confirmed by laboratory investigations.

Clinical suspicion of neonatal sepsis should be considered in presence of the risk factors (see above). Presence of more than one risk factor especially in association with

prematurity makes sepsis more likely. It should be also suspected in any mechanically ventilated baby who shows a clinical deterioration or persistent metabolic acidosis.

Early manifestations of neonatal sepsis are usually vague and nonspecific. The condition should be considered in any baby who is ***not doing well or sick*** with lethargy, poor suckling, vomiting, fever or hypothermia. In these clinical situations, hospitalization, investigations and immediate parenteral combined antibiotic therapy are indicated.

Late manifestations or complications of neonatal sepsis are usually related to different systems. Serious focal infections may become evident as CNS (meningitis), respiratory (pneumonia), urinary (pyelonephritis), digestive (hepatitis, necrotizing enterocolitis) or skeletal (septic arthritis). Careful search for all these infections should be made. Septic arthritis of the hip should be considered when the movement of one lower limb is limited or painful and diagnosis can be confirmed by ultrasound. Other serious manifestations or complications should be expected and excluded. Sclerema is particularly fatal.

Late manifestations or complications of neonatal sepsis

Serious focal infections: Meningitis, pneumonia, pyelonephritis, hepatitis, septic arthritis.
Septic shock: Cold extremities, skin mottling, poor capillary refill, tachycardia, hypotension.
Septic renal failure: Oliguria, oedema, acidotic breathing.
Serious bleeding (DIC): Purpura, bleeding from puncture sites, necrotic skin patches.
Sclerema: Skin hardening starting over limbs and extending to trunk and face (fatal).

2. *How to confirm the diagnosis?*

With clinical diagnosis of neonatal sepsis, laboratory investigations are indicated to confirm the diagnosis and to identify the causative organism.

Laboratory confirmation is usually made by simple tests as complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Positive 2 tests indicate infection in 90% of cases and 3 tests in 97% of cases.

Laboratory findings suggestive of neonatal sepsis

Total white cell count below 5000/mm^3 or above 30000/mm^3.
Band count above 10% or band/total neutrophil ratio above 0.2.
Toxic granulations in neutrophils.
ESR above 15 mm/first hour.
CRP above 20 mg/liter.
Elevated serum level of cytokines (as interleukin-6 and interleukin-8).

Identification of the causative organism is made by appropriate cultures (blood, urine, CSF and tracheal aspirate). It is important to emphasize that positive cultures are *not* necessary for diagnosis especially when clinical suspicion is considerable and nonspecific laboratory tests are suggestive.

6. Neonatal Vomiting

Vomiting in doing well baby	Vomiting in sick baby
Amniotic gastritis	**Surgical emergencies**
Swallowed maternal blood	Tracheoesophageal fistula
Feeding disorders	Congenital intestinal obstruction
Gastroesophageal reflux	Acquired intestinal obstruction
Congenital pyloric stenosis	
Cow's milk protein intolerance	**Serious medical conditions**
	Serious infections
	Increased intracranial pressure
	Inborn errors of metabolism

Any normal neonate or infant may regurgitate or vomit once or even twice a day. This occasional vomiting should not be mistaken with the frequent or persistent vomiting which should be taken with concern.

Clinical evaluation should include the general condition, onset and characters of vomiting and the associated clinical manifestations.

Laboratory evaluation is individualized and depends on the most likely clinical diagnosis.

Possible investigations of neonatal vomiting

Barium swallow or radio-opaque catheter into the stomach: Suspected tracheoesophageal fistula.
Plain x-ray abdomen, erect position: Suspected intestinal obstruction.
Cranial ultrasound: Suspected increased intracranial pressure.
Sepsis screen: Suspected neonatal septicemia.
Metabolic screen: Suspected inborn errors of metabolism.
Barium esophagography under screen: Suspected gastroesophageal reflux.
Barium meal: Suspected pyloric stenosis.

A) VOMITING IN DOING WELL BABY

In this group, vomiting is the only clinical manifestation and it is never bile-stained. Otherwise, the baby looks well with good activity and suckling power. There is no fever, abdominal distention, disturbed consciousness, convulsions or respiratory distress.

1. Amniotic gastritis: Swallowed amniotic fluid may lead to gastric irritation and vomiting during *the first few feeds*. The vomiting is usually mucoid but it may be blood-streaked. The condition usually subsides during the first day or two.

2. Swallowed maternal blood: Bloody vomiting during the *first day or two* is mostly due to swallowed maternal blood during delivery. The condition is usually associated with bloody stool. The condition is not associated with anemia or bleeding from other sites (see neonatal bleeding).

3. Feeding disorders: Overfeeding and/or faulty feeding is the most common cause of neonatal vomiting. In case of overfeeding, vomiting occurs shortly after feeding and may be accompanied with colics and frequent bowel movements. Failure of eructation of swallowed air or vigorous manipulations after feeding may lead to vomiting. Careful dietetic history is very important in every case of neonatal vomiting in doing well babies.

4. Gastroesophageal reflux: This common problem of neonates and infants characterized by persistent relaxation of the lower esophageal sphincter and reflux of gastric contents into the esophagus. Other terms as chalasia or hiatal hernia (partial thoracic stomach) may be used. Vomiting usually starts during the *first week*. It characteristically occurs after feeding when the infant is in horizontal position and after he has been returned to his crib. The duration and effects of vomiting are related to the severity of the condition: In ***mild cases***, the condition may improve over several weeks with simple positioning and medical treatment. In ***moderate cases***, symptoms persist throughout infancy with frequent recurrent aspiration pneumonia. Other causes of recurrent aspiration, as H-type tracheoesophageal fistula and cricopharyngeal incoordination should be considered. In ***severe or persistent cases,*** symptoms continue in early childhood may be up to the age of 4 years. In these patients, chronic cough and wheezing may be the main presentation.

Radiological diagnosis is made by a barium esophagography under screen. Retrograde filling of the dilated esophagus can be demonstrated. Partial thoracic stomach (hiatal hernia) may be demonstrated.

5. Congenital pyloric stenosis: In this condition, vomiting usually starts in the *second or third week* and it becomes projectile within another week. It occurs shortly after feeding and it contains only gastric contents but never bile-stained. It may be accompanied with constipation, dehydration and weight loss. On examination, the gastric peristaltic waves may be visible immediately after feeding and before vomiting. A pyloric mass may be palpated midway between the umbilicus and right costal margin just lateral to the right rectus. Diagnosis is confirmed by barium meal, which demonstrates the dilated stomach, fine elongated pyloric canal (string sign) and the hypertrophied pylorus (pyloric tumor).

6. Cow's milk protein intolerance: It is occasionally the cause of vomiting in neonates and young infants. It should be considered in bottle-fed infants especially when vomiting is associated with colic and diarrhea. Diagnosis is confirmed by the response to a therapeutic trial of withdrawal of cow's milk and prescribing a hypoallergic soy protein milk.

B) VOMITING IN SICK BABY

In this group, vomiting may be bile-stained and is usually associated with other clinical findings as poor suckling, fever, disturbed consciousness, convulsions or abdominal distension. The baby is sick and usually necessitates hospitalization. Vomiting is caused by either a surgical emergency or a serious medical condition.

(a) Surgical emergencies

1. Tracheoesophageal fistula (TEF): It should be suspected at birth when there is unusual drooling from the mouth or with inability to pass a catheter into the stomach. Vomiting occurs with the *first feed* in a characteristic way: after one or two swallows there is vomiting, coughing, choking and cyanosis. The picture is repeated with every trial of feeding leading finally to aspiration pneumonia. Immediate radiological studies are essential. Radiological diagnosis is made by failure to pass a radio-opaque catheter into the stomach and the catheter is shown coiled in the upper esophageal pouch. There are 5 types of tracheoesophageal fistula (see Basic Pediatric Radiology). The most common type is atresia with lower fistula (85%) followed by atresia without fistula (10%). Other associated anomalies are common including the ***VATER syndrome*** (vertebral and vascular defects, tracheoesophageal fistula with esophageal atresia, renal dysplasia and renal defects).

2. Congenital intestinal obstruction: Vomiting usually starts in the *first day or two* in high obstruction and few days later in low obstruction. The vomiting is frequent, copious and bile-stained and is usually associated with abdominal distension and constipation. An urgent x-ray of the abdomen (erect position) is essential for diagnosis. In high obstruction (e.g. duodenal atresia), the double-bubble and double-fluid level can be demonstrated. In low obstruction (e.g. malrotation and volvulus), multiple fluid levels and marked abdominal distension are evident (see Basic Pediatric Radiology). The condition should be differentiated from acquired intestinal obstruction whether mechanical or functional. Intestinal perforation and pneumoperitoneum may occur in neglected cases.

Causes of congenital intestinal obstruction

High obstruction	Low obstruction
Duodenal atresia	Jejunal or ileal atresia
Annular pancreas	Malrotation and volvulus
Congenital fibrous band of Ladd	Intestinal duplication
	Meconium ileus
	Hirschsprung disease
	Imperforate anus

• In meconium ileus, there is no multiple fluid levels but the distended small bowel may be granular appearance or may show tiny bubbles mixed with meconium.

3. Acquired intestinal obstruction: ***Functional obstruction*** (paralytic ileus) is a common problem which may occur with severe hyaline membrane disease, neonatal septicemia, meconium or mucous plugs and necrotizing enterocolitis. ***Mechanical obstruction*** may also occur as in intussusception, strangulated inguinal hernia, mesenteric thrombosis and necrotizing enterocolitis. In acquired obstruction, the onset of vomiting is usually not during the first few days. Necrotizing enterocolitis is a serious disease affecting mainly the sick premature babies in neonatal intensive care units. Predisposing factors include perinatal asphyxia, polycythemia, early feeding, hyperosmolar feeds and umbilical vessel catheterization. The disease starts with increasing gastric aspirates and vomiting which is usually bile-stained. Abdominal distension and bloody diarrhea quickly follow. Intestinal perforation and peritonitis are common complications. Septic and hypovolemic shock may also occur and the baby may collapse or die. Plain x-ray of abdomen shows multiple fluid levels and may be intramural gas (pneumatosis intestinalis), which is characteristic. If perforation occurs, pneumoperitoneum can be demonstrated (see Basic Pediatric Radiology).

(b) Serious medical conditions

1. Serious infections: Septicemia, pneumonia and meningitis present in early stages with nonspecific manifestations as lethargy, poor suckling, vomiting, fever or hypothermia. The possibility should be considered in any baby who is not doing well and sepsis screen should be made (see neonatal sepsis).

2. Increased intracranial pressure: Vomiting with bulging fontanel and other neurological manifestations as disturbed consciousness or convulsions should suggest the condition. Hypoxic ischemic encephalopathy, intracranial hemorrhage and neonatal meningitis are the main causes. Cranial ultrasound and lumbar puncture are important for diagnosis (see neonatal convulsions).

3. Inborn errors of metabolism: The possibility should be considered in any newborn with unexplained vomiting. Exclusion of surgical emergencies and other serious medical conditions should be the first step. The baby is usually normal at birth and symptoms appear after a few days of milk intake. Organic acidemia and hyper-ammonemia are the main causes (see neonatal convulsions). ***Congenital adrenal hyperplasia*** should be considered in any newborn with severe vomiting leading to weight loss and dehydration. The possibility becomes great when serum electrolytes show severe hyponatremia and hyperkalemia. In females, virilized external genitalia (ambiguous genitalia) is usually evident but in males, the genitalia is normal and the diagnosis is more difficult (see also adrenocortical disorders and intersex).

7. Neonatal Bleeding

Bleeding in doing well baby	Bleeding in sick baby
Swallowed maternal blood	Stress gastric ulceration
Hemorrhagic disease of the newborn	Consumptive thrombocytopenia
Inherited coagulation defects	Disseminated intravascular coagulation
Inherited thrombocytopenia	Necrotizing enterocolitis
Immune thrombocytopenia	Surgical emergencies

Bleeding in the newborn is a common potentially serious problem. Causes are ranging from a benign transient condition to a serious fatal illness. Initial clinical assessment should include evaluation of the general condition, onset and sites of bleeding and other associated manifestations.

Laboratory evaluation should include platelet count, prothrombin time (PT) and partial thromboplastin time (PTT). It should be remembered that normal values of prothrombin and partial thromboplastin times are higher in premature and fullterms when compared to infants and children.

Normal values of laboratory screening tests in neonatal bleeding

	Platelets count	PT (in seconds)	PTT (In seconds)
Premature baby	150.000 - 400.000	14 - 22	35 - 55
Full term newborn	150.000 - 400.000	13 - 20	30 - 45
Infants and children	150.000 - 400.000	12 - 14	25 - 35

A) BLEEDING IN DOING WELL BABY

In this group, bleeding is the main clinical manifestation. Otherwise, the infant is doing well with good activity and suckling power.

1. Swallowed maternal blood: Bloody vomiting during the *first day* is mostly due to maternal blood swallowed during delivery. The condition is usually associated with bloody stool. There is no bleeding from other sites and laboratory screening tests are normal.

2. Hemorrhagic disease of the newborn: It is a common condition that occurs in infants who are not given intramuscular vitamin K immediately after delivery. Bleeding occurs due to hepatic immaturity and transient deficiency of vitamin K dependant factors Bleeding usually starts in the *third or fourth day* and it may be gastrointestinal (bloody vomiting or bloody stool), from umbilical cord, following circumcision or oozing from puncture sites. Laboratory investigations reveals prolonged

prothrombin time and partial thromboplastin time and normal platelet count. The bleeding characteristically responds dramatically to I.V. injection of 5 mg vitamin K_1 (coagulation defects are corrected within few hours).

3. Inherited coagulation defects: The condition should be suspected when bleeding occurs in spite of routine vitamin K administration at birth. It should be also suspected when bleeding does not respond to vitamin K injection. Hemophilia A or B, Von Willebrand's disease or deficiency of other factors may be responsible. Coagulation defect depends on the deficient factor (see hematology).

4. Congenital and inherited thrombocytopenias: These conditions should be suspected when bleeding in doing well baby is associated with thrombocytopenia. Two conditions are important. ***Thrombocytopenia absent radius syndrome (TAR)*** is characterized by bleeding in the first few days of life, thrombocytopenia and associated anomalies (mainly aplasia of the radius and thumb and cardiac or renal anomalies). The main defect is absent megakaryocytes in the bone marrow. ***Wiskott Aldich syndrome*** is an x-linked recessive disease characterized by bleeding, thrombocytopenia, cutaneous eczema and immunologic deficiency (mainly Ig M) leading to increased susceptibility to infection. Megakaryocytes in the bone marrow are normal and the low platelet count is due to abnormal platelet formation or release. Significant number of cases may develop lymphoreticular malignancies.

5. Neonatal immune thrombocytopenias: These conditions occur due to passage of anti-platelet antibodies through placenta to fetal circulation, leading to platelet destruction. ***Maternal ITP or SLE*** may be the cause but more commonly it occurs due to ***isoimmune thrombocytopenia,*** which is characterized by presence of fetal antigens causing maternal sensitization and formation of platelet antibodies. The condition occurs in the first pregnancy and recurs in 80% of following pregnancies. Bleeding occurs only during *the first few days* but thrombocytopenia usually persists for 4 - 8 weeks. Diagnosis is confirmed by demonstration of anti-platelet antibodies. The condition is self-limited and exchange transfusion may be needed.

B) BLEEDING IN SICK BABY

In this group, bleeding is not the only manifestation. The baby is sick, often hospitalized, with poor activity and poor suckling.

1. Stress gastric ulceration: It is a common condition that occurs in sick babies secondary to prolonged hypoxia, shock or septicemia. Intolerance to feeding with coffee ground aspirates and bloody vomiting are the main clinical manifestations. There is no bleeding from other areas and laboratory investigations reveal a normal platelet count and coagulation factors. The condition usually responds to correction of the precipitating factors in addition to simple measures as temporary withholding of feeding, gastric wash with cold saline and administration of antacids.

2. Consumptive thrombocytopenia: With ***severe septicemia***, destruction of the circulating platelets may occur and leads to bleeding from gastrointestinal tract or other

areas. Clinically, purpura may be present and the baby looks sick. Laboratory investigations reveal a thrombocytopenia without any coagulation defect. Clinical and laboratory evidence of sepsis are usually evident. ***Congenital infections*** especially cytomegalovirus may lead to pinpoint purpuric eruption and thrombocytopenia at birth.

3. Disseminated intravascular coagulation (DIC): It is a serious disease characterized by consumption of platelets and several coagulation factors in a process of formation of minute intravascular clots. An *accompanying severe illness* is usually present and the baby appears critically sick. The main precipitating factors are severe hypoxia, shock, acidosis, hypothermia and septicemia. Clinically, in addition to bleeding from puncture sites, purpura and necrotic skin patches are common. Laboratory diagnosis depends on 3 criteria: (1) thrombocytopenia, (2) Prolonged thrombin, prothrombin and partial thromboplastin times, (3) Demonstration of fibrin degradation products (FDPs) in the peripheral blood. Prognosis is generally poor as serious internal hemorrhage and intracranial hemorrhage are common complications. The outcome depends mainly on the extension of internal hemorrhage and the control of the original precipitating factors.

4. Necrotizing enterocolitis: It is a serious disease affecting primarily the sick premature babies in neonatal intensive care units. Predisposing factors include perinatal asphyxia, polycythemia, early feeding, hyperosmolar feeds and umbilical vessel catheterization. Clinically, bile-stained vomiting, abdominal distension and bloody diarrhea are the main manifestations. Intestinal obstruction (functional or mechanical) occurs and plain x-ray on the abdomen shows multiple air-fluid levels and may be intramural gas (pneumatosis intestinalis). Intestinal perforation and peritonitis are common complications and x-ray of the abdomen shows a pneumoperitoneum. The condition should be differentiated from surgical emergencies causing bloody stool as volvulus and intussusception.

5. Surgical emergencies: Volvulus or intussusception usually present with severe vomiting, abdominal distension and bloody stool or passage of blood and mucus from the rectum without fecal matter. Plain x-ray on the abdomen reveals multiple air-fluid levels. In case of intussusception, an abdominal mass may be felt in the right upper quadrant (see also neonatal vomiting and gastrointestinal bleeding).

8. Neonatal Anemia

Blood loss	Hemolysis	Diminished RBCs production
Before or during delivery	**Acute hemolysis**	**Physiological anemia**
Fetomaternal transfusion	Rh incompatibility	of infancy
Fetofetal transfusion	ABO incompatibility	of prematurity
	G6PD deficiency	
External blood loss	Septicemia	**Pathological anemia**
From umbilical vein	DIC	Congenital infections
From GIT		Congenital leukemia
Frequent sampling	**Chronic hemolysis**	Congenital red cell anemia
	Congenital sphercytosis	Osteopetrosis
Internal blood loss	Thalassemias	Drug-induced
Intracranial hemorrhage	Sickle cell anemia	
Pulmonary hemorrhage	Enzymatic deficiency	

Anemia in the newborn is a common problem that occurs due to several unrelated conditions. Diagnosis is made when hemoglobin level of venous sample is below 14 gm/dl. It is important to know that capillary blood samples can give hemoglobin concentration 1-2 gm/dl higher than simultaneous venous samples. In severe cases, hemoglobin level may reach below 8 gm/dl. Clinical evaluation should include the onset and severity of anemia, evidence of blood loss and associated clinical manifestations.

Clinical evaluation of neonatal anemia

Severe anemia with shock and poor perfusion: Acute blood loss.
Severe anemia with jaundice: Acute hemolysis.
Anemia in critically sick baby: Septicemia, DIC.
Hepatosplenomegaly: Chronic hemolysis, congenital infections, congenital leukemia.
Anemia only in doing well baby: Physiological anemia.

Laboratory evaluation should include hemoglobin level, CBC, reticulocytic count, bilirubin level and Coombs test. Sepsis screen or screening for congenital infection may be done when clinical suspicion is strong. Bone marrow examination may rarely be needed. Skeletal survey may reveal osteopetrosis in unexplained cases.

Physiological anemia of infancy is characterized by progressive decline in hemoglobin level starting from the first week and persisting for about 8 - 10 weeks. The hemoglobin level, which is normally high at birth (16-18 gm/dl), gradually decreases and may reach to 10 gm/dl in full terms and 7 - 9 gm/dl in prematures. The condition is due to physiological absence of erythropoietin during this period. Folic acid or vitamin E deficiency may aggravate the anemia especially in prematures.

9. Neonatal Crying

Newborns and young infants cry for several reasons. It is clinically useful to classify causes into 3 groups:

1. Normal or physiological crying: A normal infants cries for about 2 hours a day at the age of 2 weeks and about 3 hours a day at 6 weeks then crying gradually decreases to one hour a day at 3 month. The main causes are:

a) Physiological needs: A baby who is underfed sleeps for shorter periods and cries at shorter intervals. Thirst may be also responsible.

b) Psychological needs: Some babies cry to gain sufficient or additional attention while others simply need to be held. Crying baby should always be picked up.

c) Environmental causes: Babies cry when they are wet or soiled. Uncomfortable diapers, tight abdominal binders, too much clothing, hot or cold environment may be the cause. Failure of eructation of swallowed air after feeding is also responsible.

2. Secondary excessive crying: Crying in excess of the expected normal range may be secondary to a transient or persistent illness:

a) Transient causes include any acute illness as otitis media, early pneumonia or septicemia, acute febrile illness, incarcerated inguinal hernia or napkin dermatitis. Careful exclusion of these conditions is important.

b) Persistent causes include milk allergy, lactose intolerance or maternal diet containing irritant foods as spices and chocolates. History should always include the maternal diet.

3. Primary excessive crying (Infantile colic): Other terms as "evening colic", "three months colic" or "paroxysmal fussing in infants" or are used to describe this common problem of newborns and young infants. Some infants seem to be more susceptible and generally described as "colicky infants". The condition usually starts in the first or second week and usually persists till the infant is three of four months. It is characterized by repeated attacks or paroxysms of excessive crying occurring mainly in late afternoon and evening. The attack begins suddenly with loud and continuous crying which may last for several hours and during it, the face is flushed, abdomen is distended and tense, hands are clenched and knees are drawn up on the abdomen. The baby may look hungry but he is not quieted for long either by feeding or picking up. Apparent relief usually follows passage of feces or flatus. The cause of the condition is unknown. Recent theory incriminates three factors; feeding, psychosocial environment and intrinsic problem in the infant. Mothers should be reassured that the condition does not reflect any serious illness and it will subside gradually to disappear at the age of 3 - 4 months.

10. Neonatal Cutaneous Lesions

Several cutaneous problems are commonly encountered in neonates and young infants. The most common lesions are:

1. Napkin or diaper dermatitis: Inflammation and erythema of the diaper area is a very common condition of neonates and young infants. The main 2 causes are contact dermatitis and monilial dermatitis:

a) Contact napkin dermatitis: It occurs due to friction and prolonged contact with urine and stool. Retained soaps may be also responsible. The diaper area becomes erythematous with fissuring, erosions and may be macerations. The eruption involves mainly the convex surfaces of buttocks, medial side of the highs and genital area but groin creases are usually spared. Secondary fungal infection (Monilia) is common.

b) Monilial napkin dermatitis: It usually follows contact dermatitis. It is characterized by intense fiery red erythema with sharply demarcated edge, which may extend to involve the whole napkin area and rises on the trunk. Small satellite lesions outside the sharp edge are characteristic of monilial napkin dermatitis.

c) Persistent diaper rash for weeks in spite of therapy should suggest other conditions as seborrheic dermatitis, acrodermatitis enteropathica and histiocytosis X.

2. Seborrheic dermatitis: It is a common chronic inflammatory disease that may start during the neonatal period. The scalp is the most common involved site where diffuse or focal scaling and crusting occur ***(cradle cap)***. The inflammatory process may involve the face, neck, retroauricular area and diaper area. A generalized form ***(Leiner disease)*** is uncommon and it is usually associated with complement deficiency.

3. Milia: They are tiny sebaceous retention cysts scattered over the face, mainly on the nose and around it. They appear as whitish opalescent pinhead-sized spots. Milia can be felt with the finger and it usually disappears within few weeks.

4. Mongolian spots: These are blue macular lesions that occur most commonly in the presacral area. They may be solitary or multiple and usually involve large areas. These lesions usually fade during the first few years.

5. Umbilical granuloma: The umbilical cord usually separates during the first or the second week. Mild infection may result in formation of moist granulation tissue at the base of the cord. The granuloma is soft, vascular and pinkish in color with mucoid or mucopurulent discharge. Cleaning with alcohol several times a day may be effective. Cauterization with silver nitrate may be necessary in persistent cases.

6. Breast engorgement: It is a common physiological process in newborns due to transplacental passage of maternal hormones mainly estrogen. Manual expression or any manipulations should be avoided; otherwise infection may occur (mastitis neonatorum). Clinical manifestations of infection include redness, swelling and pain. If an abscess develops, it should be incised and drained.

2

Growth and Development

- Assessment of growth and Development.

1. Underweight and Failure to Thrive.
2. Overweight or Obesity.
3. Short Stature.
4. Tall Stature.
5. Small Head.
6. Large Head.
7. Delayed Motor Development.
8. Mental Retardation.

Clinical Assessment

Physical growth	Motor and Mental development
Main parameters Weight Length or height Head circumference (Growth curves for each parameter are available) **Body proportions** Weight/length ratio Upper/lower segment ratio Arm span/height ratio **Body mass index (BMI)** **Bone age**	**Motor development** Gross motor skills More refined motor skills Fine motor skills **Mental development** Social development Speech development Learning ability **Sphincteric control** (No sharp demarcation between normal and abnormal)

Assessment of growth and development should be an essential step in examination of every patient. With such an assessment, a line of demarcation can be made between what is normal and what is abnormal.

A) ASSESSMENT OF PHYSICAL GROWTH

Physical growth can be simply assessed by weighing the patient, measuring the supine length (below 2 years) or standing height (above 2 years) and the head circumference. Assessment of the body proportions by calculation of some simple ratios is also important. However, it should be remembered *"there is a wide range of variations among normal infants and children"*. For this reason, growth curves were designed.

Growth curves for weight, length or height and head circumference are available in percentile values where the 50th percentile represents the average and indicates that 50°lo of normal children are below this value. 25th, 10th and 5th percentile are low normal value while 75th, 90th and 95th are high normal values. Growth curves are useful in two ways:

a) *With single measurement,* values below 5th percentile or above 95th percentile are abnormal. Abnormalities include *underweight* and *overweight*, *short stature* and *tall stature* and *small head* and *large head.*

b) With repeated or serial measurements, the growth rate or *growth velocity* can be assessed. Any normal infant or child should follow his own percentile on serial measurements. So, any deviation from the own percentile is also abnormal. Serial measurements can obviously detect early abnormalities although the patient is still lying in the wide normal range.

p Normal percentile values of weight (in kg) at different ages

	5th	10th	25th	50th	75th	90th	95th
Birth	2.5	2.8	3.0	3.3	3.6	3.8	4.0
3 months	4.4	4.8	5.3	6.0	6.5	7.0	7.3
6 months	6.2	6.6	7.2	7.8	8.5	9.0	9.5
9 months	7.5	8.0	8.5	9.0	10.0	10.5	11.0
12 months	8.4	8.8	9.5	10.0	11.0	11.5	12.0
2 years	10.5	11.0	11.5	12.5	13.5	14.2	14.7
3 years	12.0	12.5	13.0	14.5	15.7	17.0	17.7
4 years	13.6	14.2	15.5	16.7	18.0	19.3	20.2
5 years	15.2	15.9	17.2	18.7	20.0	21.7	23.0
6 years	17.0	17.7	19.0	20.7	22.4	24.3	26.3
7 years	18.5	19.5	21.0	22.9	25.0	27.3	30.0
8 years	20.4	21.4	22.0	25.3	28.0	31.0	34.5
9 years	22.2	23.4	25.4	28.0	31.4	35.5	39.5
10 years	24.3	25.5	28.0	31.4	35.5	41.0	45.0
11 years	26.5	28.0	31.0	35.0	40.5	46.5	51.5
12 years	30.0	31 .5	35.0	40.0	45.5	52.0	58.0

Normal percentile values of length and height (in cm) at different ages

	5th	10th	25th	50th	75th	90th	95th
Birth	46.5	47.5	49.0	50.5	52.0	53.5	54.5
3 months	56.5	57.5	59.5	61.0	63.0	64.5	65.0
6 months	63.5	64.5	66.0	67.5	69.5	71.0	73.0
9 months	68.0	69.0	70.5	72.0	74.0	76.0	77.0
12 months	71.5	73.0	74.5	76.0	77.5	80.0	81.0
2 years	82.5	83.5	85.5	87.0	89.0	92.0	94.0
3 years	89.0	90.5	92.5	95.0	97.5	100.0	102.0
4 years	95.5	97.5	100.0	103.0	105.5	108.0	110.0
5 years	102.0	103.5	106.5	110.0	113.0	115.0	117.0
6 years	107.5	109.5	112.5	116.0	119.0	122.0	123.5
7 years	113.0	115.0	118.0	121.5	125.0	128.0	130.0
8 years	118.0	120.0	123.0	127.0	130.5	133.5	135.0
9 years	123.0	125.0	128.0	132.0	136.0	139.5	142.0
10 years	127.5	130.0	133.5	137.5	141.0	145.0	148.0
11 years	132.5	135.0	138.5	143.0	148.0	152.0	155.0
12 years	137.5	140.0	144.5	150.0	154.5	159.5	162.0

* Above mentioned values are of normal males. Values of females are slightly lower.

Normal percentile values of head circumference (in cm) at different ages

	5th	10th	25th	50th	75th	90th	95th
Birth	32.6	33.0	34.0	35.0	35.5	36.5	37.0
3 months	38.5	39.0	39.0	40.5	41.5	42.3	43.0
6 months	41.5	42.0	43.0	43.5	44.5	45.5	46.0
9 months	43.5	44.0	45.0	46.0	46.5	47.5	48.0
1.0 year	44.5	45.5	46.0	47.0	48.0	48.5	49.0
2.0 years	47.0	47.5	48.5	49.0	50.0	51.0	51.5
3.0 years	48.5	49.0	49.5	50.5	51.5	52.0	52.0

- Above mentioned values are of normal males. Values of females are slightly lower.

The percentile weight/length ratio is important to know which parameter is more affected. For instance, if the height is in the 50th percentile and the weight is in the 10th percentile, the weight is relatively low for height. In case of ***growth failure***, the ratio is important to know the type or the pattern of growth failure. If weight and length are equally affected, the infant is *small or stunted* and this means growth delay or failure to thrive. If weight is more affected than length, the infant is *wasted or marasmic* and this means a severe and rather recent illness. If height is more affected than weight, the infant or the child is dwarf or having *short stature*. In this case, other body proportions as upper segment/lower segment ratio and arm span/height ratio are important to classify short stature into proportionate and disproportionate groups (see short stature).

Body mass index (BMI) is widely accepted as the best clinical measure of underweight and overweight. It is measured as *weight (in kg) /height* ^{2} *(in meters)*. Normal value is 15-22. Percentile curves are available where values below 5th percentile indicate underweight and values above 95th indicate overweight. In case of ***overweight or obesity***, other parameters as triceps and subscapular skin fold thickness are more accurate index of adiposity because BMI cannot differentiate tissue and bone from fat

Radiological determination of **bone age** is especially important in severe long standing cases. Simple and rapid determination can be roughly made by considering the time of appearance of ossific centers. Bone age may be normal, retarded or advanced.

B) ASSESSMENT OF MOTOR AND MENTAL DEVELOPMENT

Assessment of motor development is made by evaluation of gross motor skills (in infancy), more refined motor skills (in early childhood) and fine motor skills (in late childhood). ***Delayed motor development*** (marked deviation from normal average) may occur due to mental retardation, cerebral palsy or gross environmental neglect as in rickets and malnutrition (see history and examination).

Assessment of mental or intellectual development is made by evaluation of social development (in infancy), speech development (in early childhood) and learning ability or school achievement in late childhood. ***Mental retardation*** (marked deviation from the normal average) occurs due to several genetic or nongenetic causes.

1. Underweight and Failure to Thrive

Primary growth failure	Secondary growth failure
Prematurity	**Nutritional (80% of cases)** Undernutrition Environmental deprivation and neglect
Intrauterine growth retardation Chromosomal disorders Congenital infections	**Organic causes (20% of cases)** Chronic infections (as T.B) Chronic systemic diseases: CNS, chest, heart, GIT and renal Metabolic diseases

Underweight is a *weight* below the 5th percentile for age and sex or a *body mass index* below the 5th percentile for age and sex. It is the commonest abnormality in physical growth especially in underdeveloped countries. It is mainly a problem of infancy.

- Is it primary or secondary?
- What is the degree of growth failure?
- What is the pattern of growth failure?
- What is the cause?

1. *Is it primary or secondary?*

The first question in evaluation of underweight infants should be the birth weight to know whether the growth failure is of prenatal or postnatal onset.

1. Primary growth failure is characterized by a ***"low birth weight"*** and it indicates a prenatal onset of growth failure. In this case, asking about the gestational age (premature or full term) is also important to know whether the cause is prematurity or intrauterine growth retardation.

2. Secondary growth failure is characterized by a "normal birth weight" and it indicates a postnatal onset of growth failure. In this case, detailed dietetic history is very important to know whether the cause is nutritional deficiency (80% of cases) or organic diseases (20% of cases).

2. *What is the degree of growth failure?*

The degree of growth failure can be estimated by the ratio of the actual weight to the expected normal weight for age and sex. For instance, if a one-year infant is weighing 5 kg and his expected normal weight is 10 kg, the degree of underweight is 50%.

3. What is the pattern of growth failure?

The pattern of growth failure can be assessed by considering the weight/length ratio and determining if they are proportionately affected or not.

1. Small or stunted infant: In this case, weight and length are proportionately affected and the infant looks small or stunted for his age. With serial measurements (or if previous records are available) these infants can be divided into 2 subgroups. In infants with ***growth delay***, the patient is gaining weight at a rate slower than the expected normal rate while in those with ***failure to thrive***, the growth is arrested and the patient fails to gain weight.

2. Wasted or marasmic infant: In this case, the weight is markedly affected than the height and the infant looks wasted with loss of subcutaneous fat and muscle wasting. Severe nutritional deficiency and severe chronic infection are the main causes.

4. What is the cause?

Identification of the cause of underweight and failure to thrive requires careful clinical evaluation, hospitalization and may be several investigations.

1. Clinical evaluation: Detailed history and complete physical examination can frequently provide clues about the causative disease.

History and examination of underweight and failure to thrive

History

Detailed nutritional history: Number of feeds, amount/feed, and types of foods.
History of chronic illness as chronic cough, chronic vomiting or chronic diarrhea.
Family history of previously affected siblings or metabolic disease.

Examination

Mental retardation: Chromosomal abnormalities or aminoacidopathies.
Intense eye to eye contact: Nutritional or environmental deprivation.
Abnormal features: Chromosomal abnormalities.
Chest examination: Chronic chest disease.
Cardiac examination: Congenital heart disease.
Hepatomegaly or hepatosplenomegaly: Congenital infection or metabolic disease.
Renal mass: Obstructive uropathy and chronic renal failure.
Abnormal odor of urine: Aminoacidopathies.

2. Hospitalization: Hospitalization for 2 weeks is important especially in severe cases for observation of food intake, infant's behavior and weight gain. In up to 80% of cases, the cause is undernutrition and environmental neglect. Hospitalization of these cases results in adequate weight gain and several investigations become unnecessary. Failure to gain weight after a trial of feeding for 2 weeks in a hospital requires further evaluation.

3. Investigations: When history and physical examination suggest a certain etiology, investigations should be directed to confirm the suspected disease. For instance, ***chronic vomiting*** necessitates radiological studies of the upper gastrointestinal tract (barium swallow, barium meal) and evaluation of renal function and acid-base status (blood urea, creatinine and blood gases). ***Chronic diarrhea*** requires examination of the stool (pH, fat content, protozoal infection) in addition to other investigations as sweat chloride test, intestinal mucosal biopsy and may be radiological studies (see chronic diarrhea). ***Chronic cough*** requires a chest x-ray, tuberculin test, sweat chloride test, sedimentation rate and immunoglobulins. Suspected ***cardiac disease*** requires echocardiography and ***hepatomegaly or hepatosplenomegaly*** requires abdominal ultrasound, evaluation of liver function, screening for congenital infections and metabolic screen for aminoacidopathies.

When history and examination fail to suggest a specific etiology and an adequate trial of feeding in a hospital fails to show adequate weight gain, other investigations are needed to identify the causative disease.

Investigations of unexplained underweight and failure to thrive.

Intestinal malabsorption without diarrhea: Stool fat content, serum carotine level.
Chronic renal failure: Blood urea and creatinine.
Renal tubular acidosis: Blood gases to detect chronic metabolic acidosis.
Aminoacidopathies: Urine aminoacid screen, blood gases.
Chromosomal abnormalities: Karyotype for detection of trisomies and deletion syndromes.

Nutritional and environmental failure to thrive

This group accounts for up to 80% of cases of failure to thrive. Several factors usually exist and interact to produce illness. ***Poverty*** is a main contributing factor as most cases are belonging to low socioeconomic classes where adequate nutrition is not available. ***Family problems*** may be also responsible as low intelligence of parents, marital discord, drug addiction of a parent, divorce and single parent family. ***Child abuse*** whether physical or in form of withholding of food may be occasionally responsible. ***Feeding disorders***, as poor feeding techniques and provision of inappropriate foods are frequently responsible. Exploration of all these factors is important and repeated unhurried interviews with parents may be necessary.

Clinically, in addition to underweight and failure to thrive, other findings are commonly present and should suggest the diagnosis. Features of ***emotional deprivation*** as intense eye-to-eye contact, apathy or withdrawing behavior are frequently evident. ***Disorders of oral intake*** as anorexia, voracious appetite (polyphagia) or pica (diverted appetite to wall paints, dirt or mud etc.) are also common. ***Poor hygiene*** with cradle cap, napkin dermatitis and repeated acute infections are frequently present.

2. Overweight or Obesity

Simple (exogenous) obesity	Organic (endogenous) obesity
Several factors cooperate Genetic factors Environmental factors Psychological factors	Cushing syndrome Turner syndrome (in females) Klinefelter syndrome (in males) Laurence Moon Biedle syndrome Pradder Willi syndrome Albright's syndrome

Overweight or obesity is a *weight* above 95th percentile for age and sex or a *body mass index* above the 95th percentile for age and sex.

1. Is it simple (exogenous) or organic (endogenous)?

Clinical differentiation can be simply made by measuring the *length*.

1. Simple obesity: It accounts for the majority of cases. Clinically, both weight and height are above normal and the patient looks large sized for age and sex. Mentality is normal and no other abnormal findings.

2. Organic obesity: It accounts for a small percentage of cases. Clinically, the length is not above normal but in contrary the patient is frequently short. Mental retardation may be present and hand anomalies may occur.

2. What is the cause?

In **simple obesity**, no single factor can be incriminated and in most cases more than one factor coexist. A *genetic factor* is important as many obese children belong to obese parents. *Environmental factors* as overeating and diminished physical activity are also important. *Psychological factors* are also important as many children may respond to stresses by overeating. In addition, a vicious circle may occur as obese children may not share in physical activities with other children and more weight gain occurs.

In **organic obesity**, evaluation of mentality and hand examination are particularly important (see below). ***Cushing syndrome*** due to prolonged use of exogenous steroids is probably the most common organic cause. Chromosomal karyotyping is important to diagnose ***Turner syndrome*** in females and ***Klinefelter syndrome*** in males.

Causes and diagnostic features of obesity and mental retardation

Laurence-Moon-Biedl syndrome: Polydactyly, retinitis pigmentosa, hypogonadism.
Pradder Willi syndrome: Brachydactyly, hypotonia, hypogonadism, ± diabetes.
Albright's syndrome: Brachydactyly, osteodystrophy, hypoparathyroidism (hypocalcemia).

3. Short Stature

Proportionate short stature	Disproportionate short stature
Normal variant	**Short limbs**
Genetic (familial) short stature	Achondroplasia
Constitutional delay in growth and adolescence	Hypochondroplasia
Endocrinal causes	Chondroectodermal dysplasia
Growth hormone deficiency	Osteogenesis imperfecta
Hypothyroidism	Mucopolysaccharidosis
Hypocortisolism	**Short trunk**
Other causes	Morquio's disease
Chronic systemic diseases	Spondyloepiphyseal dysplasia

Short stature is a height below the 5th percentile for age and sex. The most common causes are normal variants and endocrinal causes especially growth hormone deficiency, hypothyroidism and hypercortisolism due to prolonged use of steroids.

- Is it proportionate or disproportionate?
- What is the cause?

1. *Is it proportionate or disproportionate?*

Clinical differentiation between proportionate and disproportionate short stature is simply made by measuring the body proportions. ***Upper segment/lower segment ratio*** is 1.7 at birth, 1.3 at 3 years and 1.0 at 7 years. Lower segment is measured from symphysis pubis to the floor and upper segment is derived by subtracting the lower segment from the total height. ***Arm span/height ratio*** equals 1.0 between 8 - 12 years. During the first 7 years, arm span is normally 3 cm less than the height.

In **proportionate short stature** normal values are usually obtained, while in **disproportionate short stature** abnormal values are obtained. Short arm span and short lower segment indicates short limbs, while short upper segment indicates a short trunk.

Body proportions in disproportionate short stature

Ratio	Short limbs	Short trunk
Upper segment/lower segment ratio	High	Low
Arm span/height ratio	Low	High

2. What is the cause?

A) PROPORTIONATE SHORT STATURE

In proportionate short stature, ***initial clinical assessment*** should include:

- Height of family members (parents and siblings).
- Examination of the child to exclude chronic systemic diseases as chronic chest, heart, intestine, liver, CNS or hemolyic anemia.
- Assessment of growth velocity: When previous growth records are available, the growth velocity can be immediately assessed. The child who is growing at a normal rate (more than 5 cm/year) is unlikely to have an endocrinal cause of short stature. When previous records are not available and the height is just below the 5th percentile, a period of *follow-up for at least 6 months* is required to estimate the growth velocity. Endocrinal causes are usually associated with a growth velocity less than 5 cm/year.

Initial laboratory investigations should include:

- Evaluation of renal function to exclude chronic renal failure.
- Measurement of T_3, T_4 and TSH to exclude hypothyroidism.
- Determination of bone age (see Basic Pediatric Radiology).

Laboratory testing for growth hormone deficiency is only indicated in presence of significant retardation of bone age and growth velocity less than 5 cm/year. In proved deficiency, further investigation may be needed to identify the cause especially in acquired cases to exclude brain tumors.

Chromosomal karyotype in females with unexplained short stature should be made to exclude Turner syndrome.

(a) Normal variants

More than 90% of children with short stature are normal and they grow normally (more than 5 cm/year) at or just below the 5th percentile.

1. Genetic (familial) short stature: In these children, one parent at least is short. Bone age is normal and puberty occurs at the usual age. The ultimate adult height is short or midway between the heights of both parents.

2. Constitutional delay of growth and adolescence: In these children, the height of both parents is normal but history of slow growth in childhood in other family members may be obtained. Bone age is delayed and puberty will be also delayed. Because of delayed bone age and puberty, the predicted ultimate adult height is normal.

(b) Endocrinal causes

Endocrinal causes of short stature are considered when growth velocity is below normal (less than 5 cm/year) and bone age is significantly retarded.

1. Growth hormone (GH) deficiency: About 5% of children with short stature have GH deficiency. The condition is either congenital or acquired.

a) ***Congenital GH deficiency*** may be idiopathic or associated with pituitary dysgenesis. The onset of short stature is usually not before the age of one year. Mentality is normal and features are fine. The condition should be suspected in presence of micropenis or midline defects as cleft lip, cleft palate or single central incisor.

b) ***Acquired GH deficiency*** occur secondary to brain tumors (as craniopharyngioma or pituitaty edema), basilar skull fracture, tuberculous meningitis or radiation therapy. Presence of other neurological signs or visual complaints should suggest the possibility. The onset of short stature is usually recent in an older child.

Laboratory diagnosis of GH deficiency depends on the presence of GH level below 6 ng/ml after stimulation or provocation tests. *Exercise screening test* is made by measuring the level of GH after exercise for 20 minutes. In case of positive results (level below 6 ng/ml), the pharmacological stimulation tests are indicated. Diagnosis is made in presence of at least 2 positive tests.

Pharmacological provocation tests for diagnosis of GH deficiency

Test	Dose	Route	Time of sampling	Normal GH value
Glucagon test	0.5 mg/kg	I.M.	After 2 - 3 hours	Above 8 ng/ml.
Arginine test	0.5 mg/kg	I.V.	After 30 - 60 minutes	Above 8 ng/ml.
Insulin test	0.1 unit/kg	I.V.	After 30 - 60 minutes	Above 8 ng/ml.
L-dopa test	12.5 mg/kg	Oral	After 30 - 60 minutes	Above 8 ng/ml.

- Positive result is a growth hormone level below 6 ng/ml in 2 tests.

2. Hypothyroidism: Thyroid hormone deficiency should be routinely excluded in every case of short stature because simple therapy is available. The condition may be congenital or acquired. (see endocrinology). Acquired hypothyroidism may present in childhood with short stature and clinically the features are not coarse as in congenital cases. School underachievement may be an associated complaint. Diagnosis is confirmed by presence of thyroid hormone level (T_4) below 6 microgram/dl.

3. Hypercortisolism: Prolonged use of exogenous steroids as in treatment of nephrotic syndrome or chronic asthma is usually associated with growth failure. Clinically, obesity with moon face is obvious.

4. Other endocrinal causes: Diabetes mellitus, diabetes insipidus and aldosterone excess are also associated with growth failure.

(c) Chronic systemic disease

Chronic systemic illness should be also considered especially when weight and height are equally affected. Chronic chest, heart, intestine, liver, CNS or chronic hemolytic anemia should be excluded. Chronic renal failure in particular should be routinely excluded because growth failure may be the only presentation.

B) DISPROPORTIONATE SHORT STATURE

In disproportionate short stature, ***clinical assessment*** should include:

- Limb examination to determine which segment is affected. Proximal shortening of humerus and femur is called *rhizometic* and it is the commonest type. Middle segment shortening of ulna and radius, tibia and fibula (*mesomelic*) and terminal shortening of fingers (*acromelic*) are rare. Limb examination should also include a search for deformities and anomalies especially polydactyly.
- Head examination especially for head circumference and coarse features
- Skin examination especially for ectodermal dysplasia
- Chest examination for rib shortening and heart for congenital heart disease.

Skeletal survey is important for precise diagnosis.

1. Achondroplasia: It is the most common cause of short-limbed short stature. It is transmitted as an autosomal dominant disease but 50% of cases represent a new mutation. The essential *clinical triad* is short limbs, large head and normal trunk. The shortening of limbs is proximal (rhizomelic). Mentality is normal and neuromuscular development is also normal (see Basic Pediatric radiology and Short Atlas in Pediatrics).

2. Hypochondroplasia: The two main differences from achondroplasia are: (1) features are not prominent and (2) head is normal and not large.

3. Chondroectodermal dysplasia (or Ellis Van Creveld syndrome): It is characterized by short limbs (mainly mesomelic), ectodermal dysplasia (affecting teeth, hair and nails), polydactyly (of hands and feet) and congenital heart disease (in 50% of cases, mainly atrial septal defect). The condition should be differentiated from other causes of short limbs and polydactyly especially asphyxiating thoracic dysplasia, which is characterized by marked shortening of ribs.

4. Osteogenesis imperfecta: It is a group of disorders characterized by osteoporosis and excessive bone fragility leading to multiple fractures. The multiple fractures usually heal wrongly leading to severe deformities and shortening of limbs. Blue sclera and hearing defects are common. There are 4 types. ***Type I*** is the most common and it is transmitted as an autosomal dominant disease. The fractures are early and severe but the disease is nonlethal (normal life expectancy). Types II and III are lethal (see Basic Pediatric Radiology and Short Atlas in Pediatrics).

5. Mucopolysaccharidoses: It is a group of lysosomal disorders characterized by multisystem involvement and skeletal changes known as dysostosis multiplex. It causes shortening of limbs and to less extend some shortening of the trunk. ***Type I (hurler disease)*** is the most common and the most severe form. It is characterized clinically by short stature, coarse features, cloudy cornea, claw hands, hepatosplenomegaly and mental retardation. Type IV, on the other hand, causes mainly shortening of the trunk and is known as Morquio's disease. (See Basic Pediatric Radiology and Genetic Disorders).

4. Tall Stature

Proportionate tall stature	Disproportionate tall stature
Genetic or familial tall stature	Marfan syndrome
With simple obesity	Homocystinuria
Precocious puberty	Congenital contractural arachnodactly
Hyperthyroidism	Klinefelter syndrome
Growth hormone excess	Sotos syndrome (cerebral gigantism)

Tall stature is a height above the 95th percentile for age and sex. The initial step in clinical evaluation should be measurement of the body proportions to differentiate between proportionate and disproportionate groups.

A) PROPORTIONATE TALL STATURE

In this group, body proportions are normal. The most important points in clinical evaluation are to measure the height of parents, to weigh the child and to search for features of precocious puberty.

1. Genetic or familial tall stature: It is by far the most common cause where the child is tall because his parents are normally tall. The growth velocity is normal.

2. Tall stature with simple obesity: Overeating usually leads to obesity and tall stature. Growth velocity may be rapid.

3. Precocious puberty: Examination for early appearance of secondary sexual characters should be a routine in every case of tall stature to exclude precocious puberty.

B) DISPROPORTIONATE TALL STATURE

In this group, limbs are relatively long.

1. Marfan syndrome: It is characterized by long narrow limbs, arachnodactyly (long fingers), scoliosis, cardiac lesion (aortic incompetence) and ocular lesion (myopia and upward lens dislocation). It is an autosomal dominant disease.

2. Homocystinuria: It is characterized by long narrow limbs similar to Marfan syndrome, ocular lesions (downward lens subluxation), mental retardation and stiff joints. Urine is positive for homocystine. It is an autosomal recessive disease.

3. Congenital contractural arachnodactyly: It is characterized by long limbs (arachnodactyly), joint contractures without ocular or CNS problems. It is an autosomal dominant disease.

4. Klinefelter syndrome: It is characterized by long limbs, small firm testes, hypogonadism and infertility. It is a chromosomal disease of males (XXY).

5. Sotos syndrome (cerebral gigantism): Large size at birth, large hands and feet, large male genitalia, hyperletorism and mental retardation.

5. Small Head

True microcephaly	Craniosynostosis
Chromosomal abnormalities	**Congenital**
Intracranial infections	Isolated disorder
Perinatal anoxia	Associated with syndromes
CNS infections in early infancy	**Acquired**
Familial microcephaly	Idiopathic hypercalcemia
	Hypophosphatasia

Small head is a head circumference below the 5th percentile for age and sex.

1. *Is it true microcephaly or craniosynostosis?*

Clinical differentiation depends on 2 features; cranial sutures and manifestations of increased intracranial pressure.

1. In true microcephaly (small brain size) the sutures are normal and no features of increased intracranial pressure. Skull x-ray reveals a small vault and CT scan usually demonstrates brain atrophy (see Basic Pediatric Radiology).

2. In craniosynostosis (early fusion of cranial sutures) the sutures are closed and manifestations of increased intracranial pressure appear (as repeated vomiting, papilloedema) because there is no space for brain growth. Skull x-ray shows increased convolutional markings (beaten silver appearance) denoting chronic increased intracranial pressure (see Basic Pediatric Radiology).

2. *What is the cause?*

1. In true microcephaly, the cause can be identified by history (perinatal anoxia, CNS infection), physical examination (abnormal features, failure to thrive) and some investigations (TORCH screening, chromosomal karyotype). In *familial microcephaly,* mental retardation is usually severe and the frontal lobe is severely affected resulting in backward sloping forehead (Camel head).

2. In craniosynostosis, the condition may be isolated or associated with syndromes. It may also be acquired in case of hypercalcemia and hypophosphatasia.

Inherited syndromes of craniosynostosis

Apert syndrome: Acrocephaly, syndactyly of all 5 fingers.
Pfeiffer syndrome: Acrocephaly, midsyndactyly, short broad thumbs and toes.
Carpenter syndrome: Brachycephaly, syndactyly and polydactyly.
Crouzon syndrome: Brachycephaly, proptosis, beaked parrot-nose, prognatism.

6. Large Head

Cranial (skull) causes	Intracanial (brain) causes
Rickets	Hydrocephalus
Achondroplasia	Subdural effusion
Mucopolysaccharidosis	Subdural hemorrhage
Hypothyroidism (cretinism)	Brain tumours
Chronic hemolytic anemia	Hydranencephaly
Familial large head	Megalencephaly, Canavan disease

Large head or macrocephaly is a head circumference above the 95th percentile for age and sex. It is a common problem of infancy.

1. *Is it of cranial or intracranial origin?*

In **cranial causes,** the head usually does not exceed its percentile on serial measurements (i.e. there is no progressive head enlargement). Moreover, the large head is not the most prominent feature where more relevant findings are usually present.

In **intracranial causes,** the head usually exceeds its percentile on serial measurements (i.e. there is progressive head enlargement). The large head is usually the most prominent feature of the patient's illness.

2. *What is the cause?*

In **cranial causes,** clinical examination can often suggest the cause of large head and the diagnosis can be confirmed by simple investigations. CT scan of the head is not indicated.

Clinical clues for diagnosis of cranial causes of large head

Rickets: Rosary beads, broad epiphyses, Marfan sign.
Achondroplasia: Short-limbed short stature, normal trunk, normal mentality.
Mucopolysaccharidoses: Coarse features, hepatosplenomegaly, mental retardation.
Cretinism: Coarse features, delayed motor and mental development.
Chronic hemolytic anemia: Pallor, jaundice, splenomegaly.
Familial large head: No other findings, one or both parents have a large head.

In **intracranial causes,** history and clinical examination can provide useful information, but CT scan of the head is essential for proper differentiation. Clinically, evaluation of mentality and transillumination of the head (positive in hydranencephaly) are important. Hydranencephaly and megalencephaly are associated with profound mental retardation while the mentality in other conditions is usually not affected.

Diagnosis of hydrocephalus

Hydrocephalus (or dilatation of the ventricular system) is caused by congenital or acquired lesions. The condition results from either obstruction to CSF circulation *within* the ventricular system (obstructive hydrocephalus) or interference with CSF absorption *outside* the ventricular system in the subarachnoid cisterns around the brain stem or subarachnoid space over brain convexities (communicating hydrocephalus). Rarely, it may result from overproduction of CSF as in papilloma of choroid plexus.

1. How to diagnose hydrocephalus?

1. In infants, before closure of fontanels, the clinical signs of hydrocephalus depend on the stage at which the diagnosis is made:

- In ***early cases***, large head (macrocephaly) or head exceeding its percentile on serial measurements (progressive head enlargement) are the only signs.
- In ***moderate cases***, other clinical manifestations appear. Wide patent bulging fontanel, separated sutures and dilated scalp veins become evident. The eyes may appear deviated downwards due to loss of upward gaze (setting sun eye sign).
- In ***severe neglected cases***, complications usually appear and include blindness, motor weakness (spasticity, clonus and exaggerated tendon reflexes) and mental retardation. Evaluation of vision, motor and mental development should be a routine step in evaluation of every case.

2. In children, after closure of fontanels, the clinical signs are those of chronic increased intracranial pressure (morning vomiting, morning headache and blurring of vision). Brain tumors are the main cause in this age group.

2. Is it congenital or acquired?

1. Congenital hydrocephalus is considered when the onset of illness is in early infancy. Aqueductal stenosis is the commonest cause and it may be x-linked. Other causes are Dandy-Walker malformation, Arnold-Chiari malformation and aqueductal compression by an aneurysm of the vein of Galen.

2. Acquired hydrocephalus is considered when the onset is delayed and occurring after a period of normal growth. The main causes are post-hemorrhagic (following intraventricular hemorrhage in prematures), post-meningitic (following bacterial meningitis) and brain tumours especially those of posterior fossa causing compression of the 4th ventricle.

3. Is it obstructive or communicating?

CT scan of the head is essential to confirm the diagnosis and to determine the level of obstruction. In **obstructive hydrocephalus** there is dilatation of ventricular system proximal to the site of obstruction. In **communicating hydrocephalus** there is generalized dilatation of ventricular system i.e. the 4 ventricles are dilated (See Basic Pediatric Radiology).

7. Delayed Motor Development

Mental retardation (genetic or nongenetic)
Chronic systemic illness (chronic chest, cardiac, intestinal, hepatic or renal)
Gross environmental neglect (rickets, malnutrition, repeated illness)
Cerebral palsy (spastic or atonic)

Delayed motor development is considered when the infant acquires the motor skills at a time beyond the expected normal range. For instance, he may support his head at 5 or 6 months (instead of 3) and sits at 9 or 10 months (instead of 6 or 7).

Limits for diagnosis of delayed motor development

Delayed head support: No head support up to the age of 5 months.
Delayed sitting: Delayed head support and no sitting up to the age 10 months.
Delayed standing: Delayed head support and sitting and no standing up to the age 15 months.
Delayed walking: No walking up to the age of 18 months.

Clinical evaluation of infants with delayed motor development should include assessment of mental development, search for chronic systemic illness and gross environmental neglect.

1. Mental retardation: Infants with mental retardation always have a delayed motor development as well. It should be remembered that the reverse is not true (i.e. delayed motor development may occur in spite of the normal mental development).

2. Chronic systemic illness: A careful and thorough examination is important to exclude a chronic systemic disease. For instance, congenital cyanotic heart diseases, chronic liver or renal diseases are commonly associated with growth failure (underweight) and delayed motor development. Chronic renal failure and renal tubular acidosis should not be missed in any patient presenting with failure to thrive and delayed motor development.

3. Gross environmental neglect: Rickets and malnutrition are common causes in low socioeconomic classes. Accurate dietetic history and exclusion of these conditions is important. Occasionally, delayed motor development is simply caused by repeated exposure to infections as repeated gastroenteritis or repeated chest infection.

4. Cerebral palsy: Delayed motor development is a common presentation of cerebral palsy. Persistence of primitive neonatal reflexes and exaggerated tendon reflexes are the most characteristic features. The muscle tone may be increased (spastic type) or decreased (atonic type). Mental retardation and epilepsy may or may not be present. Clinical diagnosis of cerebral palsy should be only made after exclusion of other causes of delayed motor development (See floppy infant and spastic infant).

8. Mental Retardation

Genetic retardation	Nongenetic retardation
Chromosomal disorders	**Prenatal causes**
Trisomies syndromes	Congenital infections
Deletion syndromes	Congenital hypothyroidism
Sex chromosome syndromes	Radiation
Inborn errors of metabolism	**Perinatal and neonatal causes**
Aminoacidopathies	Hypoxic ischemic encephalopathy
Lipidoses	Intracranial hemorrhage
Mucopolysaccharidoses	Meningitis
Congenital brain anomalies	Hypoglycemia
Hydrocephalus and spina bifida	**Postnatal causes**
Familial microcephaly	Post-meningitic
Mucocutaneous syndromes	Post-encephalitic
Tuberous sclerosis	Post-traumatic
Other syndromes	Post-hypoxic
Degenerative brain diseases	Status epilepticus
Degeneration of gray matter	Hypoglycemic coma
Degeneration of white matter	Hypernatremic dehydration
Several morphological syndromes	

Mental retardation is one of the most handicapping disorders in pediatric practice. It is estimated that 3% of population are retarded. Fortunately, the great majority of them have only mild retardation.

- How to diagnose mental retardation?
- What is the degree of retardation?
- What is the cause of retardation?
- What are the investigations to be done?

1. How to diagnose mental retardation?

Mental retardation is considered when there is a gross deviation from the normal mental development.

1. ***In infancy***, the main clinical finding is the **delayed social development.** Delayed social smile for more than 3 months, delayed laughing for more than 6 months and delayed recognition of mother for more than 9 - 10 months are signs of retardation. Delayed motor development is always present as an associated finding.

2. In early childhood, the most evident feature is the **delayed speech.** The condition is usually associated with delayed sphincteric control (see enuresis).

3. In late childhood, the main features are **learning difficulties and school underachievement.** In this case, acquired hypothyroidism should be routinely excluded.

As the diagnosis of mental retardation is very traumatic to parents, a more experienced person should be consulted first. Mental retardation should not be confused with other conditions presenting with similar features.

Conditions which should not be confused with mental retardation

In Infancy	Delayed social development due to blindness (evaluate vision). Delayed motor development due to other causes.
In early childhood	Delayed speech due to deafness (evaluate hearing). Speech disorders as stuttering or stammering.
In late childhood	School underachievement due to environmental factors. Learning difficulties due to attention deficit-hyperactivity disorder (ADHD)

* **Attention deficit-hyperactivity disorder (ADHD)** is a common behavioral disorder occurring in 5-10% of school-age children. It is characterized by poor school performance (due to short attention span and easy distractibility) and hyperactivity (the child is unable to sit still at his desk, frequently walking around, tapping and whistling). The male/female incidence is 4:1.

2. *What is the degree of retardation?*

The degree of retardation can be simply assessed by considering the onset at which clinical manifestations appear:

1. Profound and severe retardation are discovered in *infancy* by the delayed social development. Children with profound retardation need a total supervision while those with severe retardation can learn a minimal self-care. Obviously, these children will not join the ordinary schools.

2. Moderate retardation is usually discovered in *early childhood* by the delayed speech. These children also will not join the ordinary schools but they can attend "classes for trainable retarded".

3. Mild retardation is usually discovered in *late childhood* by the school underachievement and poor learning ability. Most of these children do not finish the primary education.

The diagnosis should be confirmed by assessment of the ***intelligence quotient (IQ).*** Several tests are available for different ages. The 2 most commonly used tests are the "Stanford-Binet test" and the "Wechsler intelligence scale for children (WISC)" which are suitable for school age children. For preschool children, "modified Stanford-Binet test" and Wechsler preschool and primary scale for children (WPPSC) can be used.

Grading of mental retardation by intelligence quotient (IQ)

Degree	IQ	Remarks
Mild	70 - 51	Need "special class placement"
Moderate	50 - 36	Need "classes for trainable retarded"
Severe	35 - 20	Can learn " minimal self-care"
Profound	below 20	Need "total supervision"

IQ equals the estimated mental age x 100/chronological age.

3. What is the cause of retardation?

1. Environmental or subcultural retardation: It accounts for 90% of cases and the retardation is only mild. No organic cause can be identified and most cases belong to low socio-economic classes where many factors cooperate including malnutrition, infections, poor medical rare, lack of good relations, lack of stimulating conversations and minimal chance for good education.

2. Organic retardation: It accounts for only 10% of cases and the retardation is moderate, severe or profound. The incidence in low and high social classes is the same. In this group, although there are more than 100 known cause of retardation, the cause cannot be identified in more than 50% of cases. Proper history and thorough examination can provide some useful clues for diagnosis.

Diagnostic clues for diagnosis of organic causes of mental retardation

History
Prenatal, natal, neonatal and postnatal events (nongenetic retardation).
Family history for other affected siblings (genetic retardation).

Examination
Abnormal features (see odd-looking face): Chromosomal diseases, several syndromes.
Failure to thrive or abnormal odour of urine: Aminoacidopathies.
Eye defects as cataract: Galactosemia, congenital rubella, Lowe syndrome.
Congenital heart: Chromosomal, congenital rubella, hypercalcemia, Turner syndrome.
Hepatosplenomegaly: Congenital infections, galactosemia, lipidoses, mucopolysaccharidoses.
Microcephaly or macrocephaly: See above.

4. What are the investigations to be done?

With presence of abnormal findings suggesting a specific group, investigations should be directed according to the clinical suspicion. CT scan is only indicated in presence of progressive head enlargement.

With absence of abnormal physical features, **screening tests** are indicated to identify curable conditions. These tests include T3 and T4 (hypothyroidism), serum calcium (hypercalcemia), urine reducing substance (galactosemia), urine ferric chloride test (phenylketonuria) and urine cyanide nitroprusside test (homocystinuria).

3

Nutrition

- **Assessment of Nutritional Status.**

1. **Protein Calorie Malnutrition.**
2. **Rickets.**

Assessment of Nutritional Status

Clinical assessment	Laboratory indices
Nutritional history	**Static indices**
In breast-fed infants	Hemoglobin
In bottle-fed infants	Serum iron
In weaned infants	Serum ferritin
Growth assessment	**Functional indices**
Weight for age	Prothrombin time
Length or height for age	Platelet aggregation
Weight/length ratio	Red cell fragility
Body mass index (BMI)	Capillary fragility
Triceps skin fold thickness	**Immunological indices**
Growth velocity	T-lymphocytes
Features of nutritional deficiencies	Complement 3
Protein calorie malnutrition	Salivary IgA
Vitamin deficiencies	Leukocyte function
Mineral deficiencies	

Clinical assessment of nutritional status should be an essential step in examination of every infant or child.

- With **good nutritional history,** an alert physician can detect nutritional disorders very early at the stage of dietetic errors.
- With **growth assessment**, a good physician can detect nutritional disorders early at the stage of growth failure.
- With **routine examination**, features of nutritional disorders should be in mind and should be excluded.

DIETETIC ERROR → **GROWTH FAILURE** → **NUTRITIONAL DISORDER**

A) NUTRITIONAL HISTORY

(a) In breast-fed infants

Breast milk alone is the ideal food for infants during the first 4 - 6 months and also up to the end of the first year in addition to other foods. The nutritional, immunological and psychological advantages of breast-feeding should be explained to mothers and they should be encouraged to breast feed their babies.

Breast-feeding should start from the first day, usually 6 - 12 hours after birth, to be given every 3 hours (2 - 4 hours) throughout the 24 hours (round-the-clock feeding). Duration of feeding is usually 20-30 minutes and number of feeds varies from 5 -10 feeds/day. After adequate feeding, the infant should be satisfied and sleeps for 2 - 4 hours. The infant can use both breasts every feed during the first 3 weeks till milk secretion become adequate, then he can use one breast per feed. From the second month, a period of rest is taken from 12.00 midnight to 6.00 a.m. and number of feeds usually decrease to 5-7 feeds/day. It should be remembered that an adequate milk flow necessitates suckling the nipple and complete emptying of the breast in addition to good nutritional and psychological status of the mother.

Nutritional history of breast fed infants should include the number of feeds/day, duration of feeding, infant behavior after feeding and the mothers impression regarding the milk flow especially at the end of the day. Nutritional and psychological status of the mother is also important.

Several dietetic errors may occur in breast fed infants and if uncorrected early they will lead to nutritional disorders.

Dietetic errors in breast fed infants and their effects

Dietetic error	Effect
Scanty breast milk with no supplementation	Undernutrition (underweight)
Scanty breast milk with wrong supplementation with carbohydrates	Protein malnutrition (kwashiorkor)
Prolonged breast feeding without weaning or vitamin D supplementation	Nutritional vitamin D deficiency rickets
Prolonged breast-feeding without weaning or iron supplementation	Nutritional iron deficiency anemia.

(b) In bottle-fed infants

Nutritional history in bottle fed infants should include the following:

1. Indications for bottle-feeding: In healthy infants bottle-feeding can be given by one of 3 methods, each has its own indication:

a) ***Complementary feeding:*** Where breast feeds are completed by bottle feeds. It is indicated in *one* condition when breast milk is insufficient for normal growth (scanty breast milk secretion). In this case, the breast milk should be given first then the bottle completes the feed.

b) ***Supplementary feeding:*** Where some breast feeds are replaced by bottle feeds. It is indicated in *two* conditions; working mother (where the mother is absent part of the day) and twin delivery (where the mother's milk is not enough to feed both babies).

c) Substitutive feeding: Where breast-feeding is completely replaced by bottle-feeding. It is indicated in 3 conditions; absent breast milk secretion, chronically sick mother and mothers who are unwilling to breast feed their babies. In the latter condition, the reasons should be explored and the advantages of breast-feeding should be explained. When the mother insists, encourage her on artificial feeding and don't let her feel guilty.

2. The milk used: In infants below the age of 6 months, the milk used should be humanized milk. Above 6 months, full cream milks should be used. In infants with sugar intolerance or galactosemia, a lactose free formula should be used.

3. Number of feeds per day: It depends on the indication. In complementary feeding it is 1 - 6 feeds per day according to the degree of breast milk insufficiency. In working mothers, one or more feeds are given till the mother comes back and in twin delivery each baby receives 3 bottle feeds alternating with 3 breast-feeds.

4. Amount of milk per feed: It can be calculated by one of 2 ways:

a) Age method: It is only used in healthy infants:

- During the first week, 10 ml increase every day
  (10, 20, 30, 40, 50, 60 and 70 ml/feed)
- During the first month, 10 ml increase every week
  (70, 80, 90, 100 ml/feed)
- During the first year, 10 ml increase every month
  (120, 130, 140, 150, 160, 170, 180 etc.)

b) Weight method: It is suitable for healthy and diseased infants. The total amount per day equals 150 ml/kg/day. In infants receiving 6 feeds per day, the amount per feed equals 25 ml/kg.

It should be clear that the above-mentioned values are approximate and the actual amount taken varies from one infant to another.

5. Concentration of milk: The dried milk should be properly reconstituted to provide the proper concentration. Each one measure of milk needs 7 measures of water. Milks with big scoop (8 gm) need 60 ml water for each scoop and those with small scoop (4 gm) need 30 ml water for each scoop (see Practical Pediatric Therapy).

Dietetic errors with bottle-feeding are either underfeeding (due to infrequent feeds or diluted formulas) or overfeeding (due to frequent feeds or concentrated formulas).

c) In weaned infants

Weaning is the process of *gradual addition of foods other than milk* to the diet of the infant. It is usually made in 3 steps

1. Fresh fruit juices: The addition of fresh fruit juices (as orange, lemon or apple juices) may start at the age of 2 months. 30 -50 ml once or twice a day between milk feeds is important to provide fresh sources of vitamin C, which is deficient in breast milk.

2. Semisolid foods: The addition of semisolid foods can be started at the age of 4 months. At this time, maturation of digestive enzymes especially the pancreatic amylase is reached. Moreover, the infant can sit (with full trunckal support) to receive foods with the spoon. This stage extends from 4 months to the end of the first year.

3. Ordinary foods: Gradually introduction of ordinary foods can be given from the end of the first year.

General rules and suggested schedule of weaning

Only one new food is given at a time.
Other new foods are added one by one with an interval of 3 - 4 weeks.
The new food should be freshly prepared, properly mixed and have a good taste.
Foods should be given by the spoon and not by the bottle.
The infant's appetite is the best index of the proper amount.
When the infant refuses a specific food, it should be withdrawn temporarily.

At 4 months: Precooked cereal to replace one milk feed.
At 5 months: Milk pudding or Yogurt to replace another milk teed.
At 6 months: Vegetable soup with minced chicken to replace a third milk feed or fruits and biscuits (banana, apple, orange juice)
At 7 months: Egg yolk can be given. (egg white not before 1 year)
At 8 months: Meat can be added to vegetable soup.
At 9 months: Deserts and custard can be offered.
At 10 - 15 months: Gradual introduction of ordinary foods.

Nutritional history in weaned infants should include the onset of weaning, foods given, amount taken and how taken.

Dietetic errors in weaning includes:

- ***Faulty weaning*** on low protein high carbohydrate diet, which leads to kwashiorkor.
- ***Delayed weaning*** without iron or vitamin D supplementation in breast fed infants leads to iron deficiency anemia and nutritional rickets.

B) GROWTH ASSESSMENT

Growth is the most important functional index, of nutritional status in infants and children. Weight, length and weight/length ratio are very useful in evaluation of adequacy of nutrition. **Evaluation of growth velocity** by serial measurements of weight and length is the most useful index. During the first 4 months, the normal weight gain is 750 gm/month (i.e. 200 gm/week or 250 gm/10 days). Normal weight gain indicates an adequate nutrition while slow or rapid weight gain indicates undernutrition or overnutrition respectively.

Precise assessment may necessitate other measurements as mid-upper arm circumference and triceps skin fold thickness. These 2 indices are measured in the left upper arm and from them a more sensitive index is derived and is called arm muscle area (or AMA).

C) FEATURES OF NUTRITIONAL DEFICIENCIES

Clinical manifestations of nutritional disorders are only evident in late stages of the disease and after complete desaturation of tissue stores. A dietetic error and growth failure usually precede clinical signs.

Clinical features of nutritional deficiencies

Disorder	Clinical features
Protein calorie malnutrition	
Undernutrition	Slow growth, underweight, wasting.
Kwashiorkor	Edema, several other features.
Vitamin deficiencies	
Vitamin D	Rickets (rosary beads, broad epiphysis).
Vitamin C	Scurvy (rare).
Vitamin A	Xerophthalmia, keratomalacia, skin keratinization.
Vitamin B1	Beriberi (polyneuritis, heart failure).
Vitamin B2	Ariboflavinosis (angular stomatitis).
Niacin	Pellagra (rare).
Vitamin B12	Megaloblastic anemia.
Folic acid	Megaloblastic anemia.
Vitamin K	Hemorrhagic manifestations.
Mineral deficiencies	
Iron	Iron deficiency anemia.
Zinc	Anemia, acrodermatitis enteropathica, short stature.
Iodine	Simple goiter, endemic cretinism.

D) LABORATORY ASSESSMENT

Several laboratory indices may be used to assess the nutritional status. ***Static indices*** are simple but cannot detect marginal cases of malnutrition and cannot monitor changes in response to nutritional intervention. Nutritional deficiency is considered in presence of hemoglobin level below 10 gm/dl, serum iron below 50 mcg/dl, serum transferrin below 150 mcg/dl or serum ferritin below 18 ng/ml). ***Functional and immunological indices*** are more sensitive. Immunological indices are very useful in protein malnutrition and they can monitor changes in response to therapeutic intervention.

1. Protein Calorie Malnutrition

Total caloric deficiency (Undernutrition)	Protein deficiency (Protein malnutrition)	Mixed forms
Nutritional dwarfism Nutritional failure to thrive Nutritional marasmus	Prekwashiorkor Classic kwashiorkor Complicated kwashiorkor	Marasmic kwashiorkor

Protein caloric malnutrition is a major health problem in underdeveloped countries. ***Poverty and ignorance*** are the 2 main contributing factors. Protein calorie malnutrition is commonly seen in low socioeconomic classes especially in late infancy and early childhood (6 months - 2 years).

- What are the dietetic errors that lead to malnutrition?
- What are the clinical presentations?
- What are the confirmatory investigations?

1. What are the dietetic errors that lead to malnutrition?

1. In **total caloric deficiency,** the main dietetic error is ***undernutrition*** due to:

- Scanty breast milk secretion with *no* supplementation (in breast-fed infants).
- Diluted formula or infrequent feeding (in bottle-fed infants).

2. In **protein deficiency,** the main dietetic error is ***faulty weaning*** due to:

- Scanty breast milk secretion with *wrong* supplementation on low protein high carbohydrate diet as rice water, sugary fluids or starchy products.
- Sudden weaning on low protein high carbohydrate diet usually following the delivery of a new sibling.
- Prolonged restriction of milk in severe cases of gastroenteritis.

3. In **mixed forms,** both dietetic errors coexist due to:

- When an infant with undernutrition receives high carbohydrate low protein diet. (i.e. wrong supplementation of undernourished infant).
- When an infant with protein deficiency develops significant anorexia and the total intake decreases (i.e. undernutrition in kwashiorkor infant).

2. What are the clinical presentations of malnutrition?

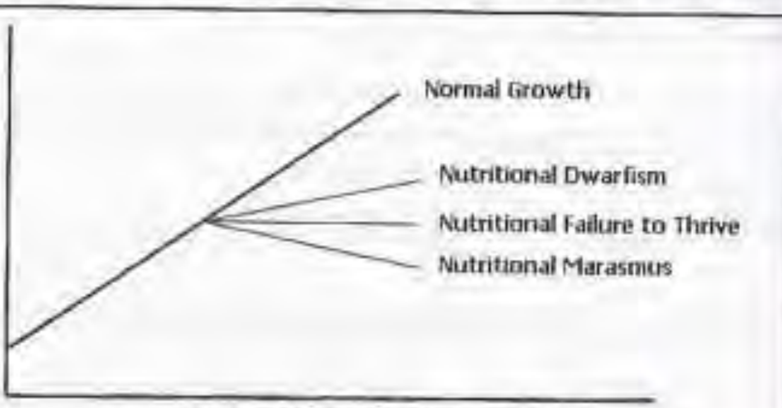
1. In total caloric deficiency, the essential feature is underweight. Other clinical manifestations depends on the degree of caloric deficiency:

a) Nutritional dwarfism: It occurs with mild caloric deficiency where the calories are not enough for normal growth. On serial measurements, the infant gains weight at a rate slower than the normal expected rate (slow growth). Clinically, both weight and length are proportionately affected and the infant looks *small or stunted* for his age.

b) Nutritional failure to thrive: It occurs with moderate caloric deficiency where the calories are just enough for metabolic maintenance. On serial measurements, the infant fails to gain weight (failure to thrive). Clinically, both weight and length are proportionately affected and the infant looks small or stunted for his age. Differentiation from nutritional dwarfism depends on serial measurements.

c) Nutritional marasmus: It occurs with severe caloric deficiency where the calories are not even enough for metabolic maintenance. On serial measurements, the infant loses weight (weight loss). Clinically, the infant looked wasted with loss of subcutaneous fat and muscle wasting. According to the degree of wasting, marasmus is divided into 3 clinical grades:

- I: Loss of subcutaneous fat over abdominal wall.
- II: Loss of subcutaneous fat over the buttocks and thighs.
- III: Loss of subcutaneous fat over the face (senile or monkey face).



Patterns of Growth in Undernutrition

In all the forms of undernutrition, the degree of underweight is related to the duration of illness (see also underweight).

2. In protein deficiency, the essential feature is edema. Other clinical manifestations depend on the degree and duration of protein deficiency.

a) Prekwashiorkor: It is an early form, which occurs within 1-3 weeks of protein deficiency. The main clinical feature is fullness of the cheeks, which is misinterpreted by the mother as a sign of good health. Mild edema of the feet may be also present.

b) Classic kwashiorkor: The constant features are edema (face, dorsum of hands and feet), mental changes (apathy, lack of interest), decreased muscle fat ratio and growth failure. The variable features are hair changes (hair become lighter in color, thin, sparse and easily detached), skin changes (erythema, darkening, fissuring, scaling mainly in buttocks, napkin area and lower limbs), hepatomegaly, anemia and vitamin deficiencies.

c) Complicated kwashiorkor: In addition to the classic features, serious complications occur and hospitalization becomes necessary. Severe infections as bronchopneumonia or gastroenteritis are common and may be the cause of death. Severe water and electrolyte disturbances as dehydration, metabolic acidosis and hypokalemia are common especially

with severe gastroenteritis and secondary malabsorption. *Severe anorexia* with almost total refusal of feeding may occur due to severe anemia, severe vitamin deficiencies and severe infections.

3. In mixed forms, different combinations of caloric and protein deficiency may occur. The severest form is marasmic kwashiorkor where wasting and edema coexist.

Comparison between marasmus and kwashiorkor

	Marasmus	Kwashiorkor
Cause	Severe caloric deficiency	Severe protein deficiency
Essential features	Underweight, wasting	Edema, other features
Behaviour	Alert, good appetite	Apathetic, anorexia
Metabolic functions	Not disturbed	Greatly disturbed
Prognosis	Generally good	Generally bad

3. *What are the confirmatory investigations?*

1. In total caloric deficiency, the metabolic functions are not significantly disturbed because of the balanced deficiency, so laboratory abnormalities are minimal.

2. In protein deficiency, the metabolic functions are greatly disturbed and several laboratory findings are usually present:

a. ***Hypoproteinemia:*** Total plasma protein level is low (normally, 6-8 gm/dl) and albumin is usually below 3 gm/dl (normally, 4-5 gm/dl). Gammaglobulins may be normal or elevated due to the associated infections.

b. ***Anemia:*** low hemoglobin level, serum iron and serum ferritin are common.

c. ***Hypoglycemia, hypokalemia and hyponatremia*** are common.

d. ***Secondary immunodeficiency:*** Kwashiorkor is the commonest cause of acquired immunodeficiency in underdeveloped countries. The main findings are:

- *T cell dysfunction:* Both T4 and T8 are reduced in number with more reduction in T4 resulting in low T4/T8 ratio (normal ratio is 1:2).
- *B-cell dysfunction:* It is less marked than T-cells. Circulating B-cells and antibody response may be decreased.
- *Complement dysfunction:* Reduction of several components especially C_3
- *Leukocyte dysfunction*: Chemotaxis, opsonization and intracellular killing activity are also reduced (see also recurrent chest infection).

e. ***Malabsorption:*** Chronic diarrhea due to intestinal malabsorption is common and it results from immunodeficiency, pancreatic enzyme deficiency and sugar intolerance.

2. Rickets

Nutritional rickets	Non-nutritional rickets
Prolonged breast-feeding Fresh cow's milk feeding Unexposure to sunlight	**Inherited rickets** Hypophosphatemic vitamin D resistant rickets Hypocalcemic vitamin D resistant rickets Renal tubular acidosis Cystinosis Tyrosinemia Lowe syndrome
Conditions resembling rickets Hypophosphatasia Metaphyseal dysostosis	**Rickets with chronic diseases** With chronic malabsorption With chronic liver disease With chronic renal failure With chronic antiepileptic therapy With mesenchymal tumors

Rickets is a metabolic disease characterized by defective mineralization of bones. Most cases in underdeveloped countries are nutritional in origin and mostly seen between 6 months and 2 years. However, non-nutritional causes should be considered when the onset is too early (below 6 months), too late (above 2 years) or when a chronic disorder is concomitantly present.

- How to diagnose rickets?
- Is it active or healed?
- What are the complications?
- What is the cause?

1. *How to diagnose rickets?*

The possibility of rickets should be considered in every case of large head, delayed teething, delayed motor development, tetany, chronic diarrhea or prolonged breast-feeding without vitamin D supplementation.

Clinical diagnosis of rickets depends on the presence of its skeletal manifestations. Muscular and neurological manifestations may or may not be present. For instance, in hypophosphatemic vitamin D resistant rickets, the muscular and neurological manifestations are absent.

1. Skeletal manifestations: Several changes are commonly seen:

a) Head: Large head, delayed closure of the fontanel and delayed teething.

b) *Thorax:* Rosary beads (enlarged costochondral junctions), longitudinal sulcus (vertical groove behind the rosary beads) and Harrison sulcus (horizontal groove at the lower costal margin) are the main findings. Chest deformities as flaring of lower ribs and pigeon chest (sternal protrusion) are seen in advanced cases.

c) *Limbs:* Broad epiphyses at lower ends of ulna and radius and Marfan sign (transverse groove palpated over the medial malleoli) are the main findings. Limb deformities as genu varum (bow legs) or genu vulgum (knock knees) may be seen in advanced cases. In crawling infants, deformities of upper limbs may also occur.

d) *Spine:* Correctable rounded kyphosis may be present. It is important to remember that in Pott's disease the kyphosis is angular and not corrected by extension of the back.

2. Muscular manifestations: Hypotonia of the skeletal and smooth muscles is the main manifestation and it leads to ***delayed motor development*** (delayed sitting, crawling, standing or walking) and ***abdominal distension.*** The liver and spleen may be palpated below the costal margin due to their downward displacement secondary to chest deformities and hypotonia.

3. Neurological manifestations: In early cases, anorexia, irritability and sweating may be present. In advanced cases characterized by marked calcium depletion, tetany may occur. However, tetany is considered as a complication rather than a clinical finding (see below).

2. Is it active or healed?

Presence of skeletal manifestations does not mean that the rickets is active but presence of hypotonia (muscular) or tetany (neurological) is a sign of activity. Clinically, 3 points are helpful:

- History of motor development.
- History of vitamin D intake.
- Clinical examination for the signs of latent tetany (see below).

However, accurate differentiation is made by laboratory and radiological studies. A simple plain x-ray on the region of wrist joint is sufficient to show the signs of activity or healing (see Basic Pediatric radiology). Biochemical changes of activity include a normal or low calcium, low serum phosphorus and high alkaline phosphatase level (in chronic renal failure, serum phosphorus is high).

3. What are the complications?

The following complications should be considered and excluded:

1. Tetany: It occurs due to severe hypocalcemia in neglected cases of nutritional rickets or in non-nutritional cases with hypocalcemia as chronic malabsorption, chronic renal failure or hypocalcemic vitamin D dependent rickets. Occasionally, therapy with big doses of vitamin D injections leads to rapid mobilization of serum calcium into bones and development of tetany. Clinically, it may be manifest or latent:

Clinical diagnosis of tetany

Manifest tetany (occurs with serum calcium below 7 mg/dl)
- Carpopedal spasm: The most common manifestation
  - Carpal spasm (flexion of wrist, flexion of metaphalyngeal joints, adduction of thumb)
  - Pedal spasm (planter flexion of ankle joints and toes)
- Laryngospasm: Stridor and airway obstruction (in severe cases)
- Convulsions (in severe cases)

Latent tetany (occurs with serum calcium between 7-9 mg/dl). Needs provocation tests:
- Trousseau sign: Constriction of upper arm with sphygmomanometer leads to carpal spasm
- Peroneal sign: Tapping of fibula over peroneal nerve leads to pedal spasm
- Chvostek sign: Tapping of facial nerve leads to facial contraction

Treatment is by intravenous **calcium gluconate 10%** (1 ml/kg slow I.V)

Clinical exclusion of latent tetany is important especially before prescribing vitamin D injections, which may lead to manifest tetany if latent tetany is present and overlooked. It is important to remember that hypocalcemic tetany may occur without rickets and tetany may occur due to other causes as hypomagnesemia and alkalosis.

2. Respiratory infections: Because of chest deformities, rachitic patients are more susceptible to respiratory infections as bronchitis or pneumonia.

3. Fractures: Rachitic patients are susceptible to fractures due to the generalized defective mineralization of bones.

4. What is the cause?

Identification of the cause of rickets depends on 3 criteria:
- Clinical evaluation especially the age of onset and nutritional status.
- Laboratory investigations especially serum calcium, serum phosphorus, alkaline phosphatase, acid-base balance (for detection of metabolic acidosis), evaluation of renal function (blood urea and creatinine) and urine analysis for phosphate excretion and for presence of glucosuria.
- Therapeutic response to ordinary doses of vitamin D (3000 IU/day).

A) NUTRITIONAL RICKETS

Nutritional rickets is by far the commonest cause in underdeveloped countries. It occurs due to vitamin D deficiency secondary to prolonged breast-feeding or fresh cow milk feeding without supplementation of diets rich in vitamin D. Unexposure to sunlight especially in dark colored infants is an additional factor of vitamin D deficiency. Nutritional rickets is characterized by the following:

a) Clinically, it usually occurs between 6 months and 2 years. A dietetic error is usually evident and other features of malnutrition as iron deficiency anemia are common.

b) Laboratory, low or normal calcium, low phosphorus and high alkaline phosphatase.

c) Therapeutically, it is responsive to ordinary therapeutic doses of vitamin D where signs of healing appear radiologically after 2 -3 weeks of onset of therapy.

B) INHERITED RICKETS

Three inherited renal tubular disorders are associated with rickets.

1. Hypophosphatemic vitamin D resistant rickets: This x-linked dominant disease, which is also called familial hypophosphatemia, is the second most common cause of rickets. The basic defects are marked phosphate loss in urine and defective activation of 25 (OH) D to 1,25 $(OH)_2$ D. It differs from vitamin D deficiency rickets in the following:

a) ***Clinically,*** the age of presentation is usually at one or one and half years and the main feature is bowlegs. Rachitic changes in thorax as rosary beads or Harrison sulcus are minimal or absent. Because of absent hypocalcemia, muscular manifestations (hypotonia) and neurological manifestations (tetany) are also absent. Dietetic errors or features of malnutrition are also absent. (i.e. ONLY skeletal changes in lower limbs).

b) ***Laboratory,*** serum calcium is normal, phosphorus is low and alkaline phosphatase is high. The most characteristic features are the marked phosphate loss in urine (phosphaturia) and the absent aminoaciduria, glucosuria and bicarbonaturia.

c) ***Therapeutically,*** it does not respond to ordinary therapeutic doses of vitamin D and it is treated by oral phosphate therapy and activated form of vitamin D.

2. Hypocalcemic vitamin D dependent rickets: This autosomal recessive disease has 2 types. ***Type I*** is caused by 1 alpha hydroxylase deficiency which results in selective deficiency of 1,25 $(OH)_2$ D. It is clinically, biochemically and radiologically similar to nutritional vitamin D deficiency rickets. The 2 main differences are the early onset (at 3-6 months) and the failure of response to ordinary therapeutic doses of vitamin D. It responds to 1,25 $(OH)_2$ D or the synthetic analogue one alpha hydroxy cholecalciferol. ***Type II*** is an end-organ disease characterized by generalized resistance to 1,25 $(OH)_2$ D. High doses of vitamin D are not effective.

3. Renal tubular acidosis and rickets (Fanconi syndrome): The term Fanconi syndrome does not relate to a specific disease entity but it means a proximal renal tubular acidosis in association with a metabolic bone disease leading to rickets. The main diseases leading to this syndrome are cystinosis (autosomal recessive), tyrosinemia (autosomal recessive) and Lowe syndrome (x-linked recessive).

a) ***Clinically,*** the most evident features are not the rachitic changes but the manifestations of renal tubular acidosis especially chronic vomiting, failure to thrive and repeated episodes of metabolic acidosis. The onset may be in infancy (as in tyrosinosis) or later in early childhood. In Lowe syndrome (oculocerebrorenal syndrome) mental retardation and cataract are present.

b) ***Laboratory,*** it is characterized by a hyperchloremic metabolic acidosis with normal renal function in addition to phosphaturia, aminoaciduria, glucosuria and bicarbonaturia. Serum calcium is normal, phosphorus is low and alkaline phosphatase is high.

c) ***Therapeutically,*** it responds to oral bicarbonate therapy and oral phosphate therapy. Vitamin D is also needed to prevent secondary hyperparathyroidism, which complicates oral phosphate therapy.

C) RICKETS WITH CHRONIC DISEASES

Rickets may occur as a complication of several chronic disorders.

1. With chronic malabsorption: Any condition that impairs absorption of lipids from the gut will impair the absorption of fat soluble vitamins including vitamin D. Celiac disease, cystic fibrosis and obstructive jaundice are the main causes. Clinically, chronic diarrhea should raise the possibility.

2. With chronic liver disease: Both hepatocellular and biliary diseases can lead to defective bone mineralization and rickets. In hepatocellular disease, defective hydroxylation of vitamin D leads to decreased production of 25 (OH) D. In biliary disease, steatorhea is associated with decreased absorption of vitamin D.

3. With chronic renal failure: Rickets with chronic renal failure (renal osteodystrophy) occurs due to impaired hydroxylation of 25 (OH) D and phosphate retention leading to hypocalcemia and hyperparathyroidism. Clinically, rickets above the age of 5 years should suggest chronic renal failure. Other features as short stature, anemia and hypertension are usually present. Laboratory diagnosis depends on the presence of elevated blood urea and serum creatinine levels. Serum calcium is low, phosphorus is high (very important) and alkaline phosphatase is high (see chronic renal failure).

4. With chronic antiepileptic therapy: Partial inactivation of 25 (OH) D may occur with prolonged combined therapy and leads to rickets. This type can be prevented by daily administration of 1000 IU of vitamin D.

5. With benign mesenchymal tumors: Some tumors may lead to phosphate loss and rickets and the site of origin may be difficult to detect as in bones of hands and feet, abdominal sheath or pharynx. Rickets resolves after removal of the tumor.

D) CONDITIONS RESEMBLING RICKETS

1. Hypophosphatasia: It is an autosomal recessive disease that resembles rickets radiologically. The main characteristic finding is low alkaline phosphatase activity. It has 3 forms (congenital lethal form, severe infantile form and mild childhood form). Serum calcium and phosphorus are normal.

2. Metaphyseal dysostosis: It is an autosomal dominant disease which is characterized by bowlegs, short stature and waddling gait. Serum calcium, phosphorus and alkaline phosphatase are normal and vitamin D is normal

4

Infections

- **Classifications of Infections.**

1. **Acute Fever.**
2. **Prolonged Fever.**
3. **Skin Rashes (Exanthems).**
4. **Parotid Swelling.**
5. **Lymphadenopathy.**
6. **Weight Loss and Cachexia.**
7. **Arthritis.**

Classifications of Infections

A) Etiological classification

1. Bacterial infections

- Aerobic gram-positive: Staphylococci, streptococci, pneumococci, diphtheria, listeria.
- Aerobic gram-negative: Cocci (meningococci, gonococci), bacilli (E. coli, salmonella, shigella, campylobacter, citrobacter, proteus, yersinia, serratica, klebsiella, pseudomonas, aeromonas, comamonas, vibrio cholera), coccobacilli (hemophilus influenza, brucella, bordetella, pasturella), helically coiled (borelia, treponema, leptospira).
- Anaerobic gram-positive: Clostridium tetani, clostridium botulinum, lactobacillus.
- Anaerobic gram-negative: Bacteroids, fusobacterium, anaerobic vibrios.

2. Viral infections

- Respiratory viruses: Respiratory syncytial virus, adenovirus, rhinovirus, influenza and parainfluenza viruses.
- Enteroviruses: Polioviruses, ECHO and coxsackie viruses, rotavirus, reovirus.
- Exanthem viruses: Measles, german measles, roseola infantum, erythema infectiosum, herpes simplex, varecella-zoster virus.
- Other viruses: Hepatitis viruses (A,B,C,D,E), Ebstein Barr virus (infectious mononucleosis), cytomegalovirus, arbovirus (yellow fever), mumps, rabies, cat scratch disease.

3. Other infections

- Mycoplasma infection (see pneumonia).
- Mycobacterial: Tuberculosis and other atypical mycobacteria.
- Rickettsial: Typhus, scrub typhus, rickettsialpox, rocky mountain spotted fever.
- Protozoal: Malaria, amebjasis, giardiasis, leishmaniasis, toxoplasmosis.
- Mycotic: Candidiasis, histoplasmosis, aspergillosis, nocardiosis, blastomycosis, coccidioidomycosis, cryptococcosis, actinomycosis.
- Parasitic (helmintic): Nematodes (ascaris, ankylostoma, oxyuris, strangyloids, trichuris),cestodes (tenia saginata, tenia solium, hymenolepis nana, diphyllobothrium latum), trematodes (Schistosomiasis, liver flukes).

B) Clinical classification

1. Focal Infections

• CNS • Cardiac • Respiratory • Gastrointestinal • Urinary • Skeletal • Cutaneous.

2. Systemic Infections

- Multisystem involvement and/or
- Nonspecific features (Pallor, purpura, hepatosplenomegaly, lymphadenopathy).

C) Epidemiological classification

1. According to source of Infection.

- Community-acquired infections.
- Hospital-acquired (nosocomial) infections.

2. According to spread of Infection

• Sporadic • Epidemic • Endemic.

1. Acute Fever (Short Febrile Illness)

Focal infections

CNS infections
- Meningitis
- Encephalitis
- Brain abscess

Respiratory infections
- Upper: Nasopharyngitis, otitis media, Sinusitis, tonsillitis, laryngitis
- Lower: Bronchitis, bronchiolitis, pneumonia, lung abscess, empyema

Digestive infections
- Stomatitis, gastroenteritis, hepatitis, Peritonitis, appendicitis, pancreatitis

Urinary tract infections
- Pyelonephritis, cystitis

Skeletal infections
- Osteomyelitis
- Arthritis

Cutaneous infections
- Cellulitis
- Abscess

Early exanthems should be always in mind

Fever without a focus (Simple fever)

↓

General clinical assessment

History
1. Appetite and thirst
2. Activity and playfulness
3. Reaction to parents (the mood)

Examination
1. Level of consciousness
2. Appearance: Normal or sick
3. Reaction to social stimulation: Smiles or looks anxious and irritable

↓

Looks well	**Looks sick**	**Seriously ill**
↓	↓	↓
Viremia	**Bacteremia**	**Septicemia**

Acute fever or fever of duration less than a week is a common clinical problem, which accounts for at least 25% of urgent consultations. The essential role of the physician is to differentiate between ***simple benign infections,*** which are mostly self-limited and ***serious infections,*** which are life-threatening and need urgent recognition and prompt aggressive management.

Fever is not an enemy and in fact it may be a friend. The rise of body temperature is a beneficial mechanism made by the body to enhance the physiological defensive mechanism as leukocyte migration and phagocytosis.

- What is the degree of fever?
- Is it a focal infection?
- Simple fever... Is it viremia, bacteremia or septicemia?

1. What is the degree of fever?

Fever is an elevation of body temperature above normal. The normal rectal temperature in children is 36.5 -37.8°C. Normal oral temperature is a half degree lower that the rectal temperature. New methods of measuring temperature as scalp strips and ear temperature probes may be also used.

Degree of fever in children

Mild fever: Rectal temperature of 37.8 - 38.4°C.
Moderate fever: Rectal temperature of 38.5 - 39.4°C.
High fever: Rectal temperature of 39.5 - 41.0°C.
Hyperpyrexia: Rectal temperature above 41.0°C.

- Most children can tolerate mild to moderate fever with no problems.
- With high fever or hyperpyrexia, especially below the age of 2 years, the possibility of serious bacterial infections should be considered and febrile convulsions may occur in susceptible children.

The term **"hyperthermia"** is an elevation of body temperature due to external heating (i.e. high environmental temperature). High incubator temperature in newborns and heat stroke in children are examples. So, hyperthermia is not a true fever because the elevation of body temperature is against the body desire. In case of fever the patient feels cold and extremities may be also cold while in hyperthermia the patient feels hot and extremities are also hot.

2. Is it a focal infection?

After measuring the body temperature, attention should be directed to *search for a focus of infection*. Accurate history and meticulous examination of different systems are essential. It is clinically useful to classify focal infections into simple infections and serious infections. This classification is also therapeutically useful. Simple infections can be managed at home with oral drugs while serious infections need hospitalization and parenteral drug therapy.

1. Simple infections include nasopharyngitis, otitis media, sinusitis, tonsillitis, stomatitis, laryngitis, bronchitis, gastroenteritis and cystitis. History and examination should be first directed to identify these infections.

- It is important to emphasize that streptococcal pharyngitis is quite uncommon below the age of 2 years and this diagnosis should not be simply made below this age.
- It is also important to remember that otitis media is a very common condition in infants and young children and exclusion of focal infections is not complete without examination of eardrums with otoscope.
- Skin infections, as for instance, perianal abscess should not be overlooked.

2. Serious infections as bacterial meningitis, pneumonia, pyelonephritis, peritonitis and osteomyelitis or arthritis should be thoroughly excluded.

Clinical exclusion of serious focal infections

Bacterial meningitis: Look for coma, convulsions, meningeal irritation, increased ICP.
Pneumonia: Look for respiratory distress, focal chest signs (crepitations, bronchial breathing).
Pyelonephritis: Look for loin tenderness or a swelling.
Peritonitis: Look for abdominal distension and generalized tenderness.
Osteomyelitis or arthritis: Look for focal tenderness, swelling and limitation of movements.

Finally, other 2 important remarks deserve mentioning:

1. Vomiting is not a localizing sign as it accompanies several infections of different systems (see vomiting).
2. In early focal infections (first 24 or 48 hours), the focus may not be evident at the initial examination. Re-examination after 24 or 48 hours reveals the focus of infection in up to 40% of cases.

3. *Simple fever... Is it viremia, bacteremia or septicemia?*

After exclusion of focal infections the diagnosis of simple fever can be made and because of absence of any other specific features it is also called **"isolated fever"** or **"nonspecific febrile illness".**

In case of simple fever, the most important clinical problem is how to differentiate between viral and bacterial infections. Evaluation of the general condition by the **"general clinical assessment"** is very useful. With this simple assessment, a skilled physician can often differentiate between 3 clinical entities; viremia, bacteremia and septicemia.

1. Viremia: The clinical diagnosis of viremia can be made if the fever is not high and the general clinical assessment reveals that the general condition is ***fair***. In this case, prescribing an antipyretic and re-examination after 24 - 48 hours is important because re-examination may reveal a focus of infection in up to 40% of cases.

2. Bacteremia: The diagnosis of bacteremia can be clinically made if the general clinical assessment reveals that the general condition is not fair and the patient looks sick. In this case, simple investigations as CBC, CRP and ESR are useful to confirm the presence of bacterial infection. Leukocytosis (above 15.000 cells/mm^3) or bandemia above 10% are highly suggestive. Also, CRP level between 20-30 mg/liter suggests bacterial infection. When investigations are not available or the patient cannot afford the expenses, it is reasonable to prescribe an oral broad-spectrum antibiotic as ampicillin or amoxicillin and to re-examine after 24 - 48 hours.

3. Septicemia: The clinical diagnosis of septicemia is made when the general clinical assessment reveals that the patient is ***seriously ill***. High fever or hyperpyrexia would suggest the diagnosis especially when combined with persistent vomiting, pallor, toxic look, cold extremities, mottled skin or disturbed consciousness.

- Once the clinical diagnosis of septicemia is made, urgent hospitalization, urgent investigations and immediate parenteral combined antibiotic therapy are indicated.

Investigations should include simple tests (CBC, ESR, CRP), chest x-ray, CSF examination and blood and urine cultures. Polymorphonuclear leukocytosis (above 15.000 cells/mm^3), bandemia (above 10%), toxic granulations, elevated CRP (above 20mg/litre) or elevated ESR (above 20 in first hour) are confirmatory findings.

• Septicemia is a serious condition with a high morbidity and mortality rate. During the course of illness in the hospital, attention should be given to the complications or the manifestations of advanced disease. Early detection of these complications and their prompt management can save lives of many patients.

Complications or manifestations of advanced septicemia

Serious focal infections: Meningitis, pneumonia, osteomyelitis, arthritis, peritonitis.
Acute hemolytic anemia: Due to direct destruction of red cells,
Consumptive thrombocytopenia: Due to direct destruction of platelets.
Disseminated intravascular coagulation (DIC): Due to endotoxemia, shock, acidosis.
Septic shock: A combination of hypovolemic, cardiogenic and distributive shock.
Septic acute renal failure: Due to toxemia and shock.
Toxic encephalopathy: Disturbed consciousness, convulsions, increased ICP.
Sclerema: It is a fatal complication in neonates and young infants.

Toxic shock syndrome (TSS) is an entity, which deserves mentioning. It is an acute multisystem disease caused by staphylococcal toxins. It is characterized by high fever, shock and diffuse macular erythematous rash (not purpuric) in addition to several manifestations related to different systems as vomiting or diarrhea, hyperemia of mucous membranes, renal affection, hepatic affection and altered consciousness or focal neurological signs. There are no specific laboratory findings and diagnosis is mainly clinical. Cultures are negative but antibodies against staphylococcal toxins can be detected in the sera. Treatment is by parenteral antistaphylococcal drugs and prompt treatment of shock.

Fever with a purpuric rash may indicate a serious bacterial infection in up to 20% of cases. Meningococcal septicemia is the most common but several other organisms as hemophilus influenza type b, staphylococcal, streptococcal or listeria may be responsible. Management should include urgent hospitalization, blood and CSF cultures and parenteral antibiotic therapy. However, it should be remembered that in up to 80% of cases, fever and purpuric rash are caused by viral infections. Enterovirus infection especially echovirus type 9 is probably the most common. Other viral hemorrhagic fevers as black measles, Dengue fever, Dengue hemorrhagic fever and cytomegalovirus infection should be also considered (see purpura).

2. Prolonged Fever

Infections	Non-infectious causes
Bacterial infections	**Rheumatic diseases**
Systemic infections	Rheumatic fever
Salmonellosis	Systemic rheumatoid arthritis
Brucellosis	Systemic lupus erythematosus
Listeriosis	Polyarteritis nodosa
Leptospirosis	Kawasaki disease
Tularemia	Mixed connective tissue disease
Tuberculosis	**Malignancies**
Hidden focal infections	Leukemia
Abscess (liver, perinephric, pelvic)	Lymphoma
Endocarditis, pericarditis	Neuroblastoma
Pyelonephritis	**Immune reactions**
Osteomyelitis	Drug fever
Viral infections	Serum sickness
Infectious mononucleosis	**Other causes**
Cytomegalovirus infection	Factitious fever or false fever
Human immunodeficiency virus (HIV)	Crohn disease
Hepatitis	Diabetes insipidus
Parasitic infestations	Anhydrotic ectodermal dysplasia
Malaria	Familial Mediterranean fever
Toxoplasmosis	
Visceral larva migrans	

Prolonged fever is a fever with duration of more than 10 - 14 days. Although it is not as common as short febrile illness, it causes greater concern of both parents and doctors. Fortunately, unlike adults, most cases of prolonged fever in children are caused by benign infections and the prognosis for ultimate recovery is generally good.

- Is it truly a prolonged fever?
- Is there an evident cause?
- Unexplained prolonged fever... What is the cause?

I. *Is it truly a prolonged fever?*

The complaint of prolonged fever, as any other prolonged complaint, should not be accepted without careful analysis. Parents may misinterpret normal temperature as a mild fever. Careful history may reveal that the condition represents 2 short febrile illnesses rather than a prolonged one. **Documentation of fever** is important in accepting the complaint as a true prolonged fever.

2. Is there an evident cause?

With documented prolonged fever, detailed history and meticulous examination may reveal an evident cause or at least suggest a specific disease.

History and examination in children with prolonged fever

Nonspecific findings denoting significant illness

Symptoms: Anorexia, weight loss.
Signs: Toxic look, pallor, cachexia, lymphadenopathy or Hepatosplenomegaly.

Specific findings suggesting a particular disease

Symptoms related to a specific system: CNS, chest, heart, GIT, urinary.
History of contact to an adult with chronic chest disease: ? Tuberculosis.
History of eating rabbit meat: ? Tularemia.
History of medications: ? Drug fever.
Rigors: Septicemia, pyelonephritis or malaria.
Pharyngitis: Infectious mononucleosis, cytomeglovirus, tularemia, toxoplasmosis.
CNS examination May suggest meningitis.
Chest examination: May reveal pneumonia or empyema.
Cardiac examination: May reveal endocarditis or pericarditis.
Abdominal examination: Liver (hepatitis, abscess) or loin tenderness (perinephric abscess).
Skeletal examination: Arthritis or osteomyelitis (focal tenderness).
Rectal examination: Focal tenderness suggests pelvic abscess.

With clinical suspicion of any disease, investigations should be directed to confirm or exclude the suspected disease.

3. Unexplained prolonged fever... What is the cause?

When history and physical examination fail to reveal an evident cause or to suggest a specific disease, the term **"unexplained prolonged fever" or "fever of unknown origin (FUO)"** can be used. These terms should be restricted to cases of documented fever with duration of at least 10 - 14 days.

• *In patients with good general condition* and a rather short history, simple investigations (CBC, ESR, CRP, urine analysis) can be made on an outpatient basis. Normal laboratory findings in this group indicate that the illness is mostly a benign viral infection. Reassurance and follow-up are important.

• *Patients with clinical findings indicating that the illness is significant* (see above) should be hospitalized and further investigated. Hospitalization is also indicated in those with abnormal results of initial simple investigations.

Hospitalization is useful for several reasons:

a) Documentation of fever: Temperature should be regularly measured by a reliable person to exclude the possibility of "factitious or false fever".

- *Drugs should be avoided* as much as possible to exclude the possibility of drug fever. In this case, fever will subside within 1-3 days of discontinuation of the responsible drug.

- *Close observation* for the general condition (appetite, activity, reaction to stimulation), presence of rigors (septicemia, malaria) or appearance of new symptoms or signs. Frequently, the fever may subside spontaneously without any specific therapy and even before completing the investigations.

Investigations in children with unexplained prolonged fever

Nonspecific Investigations to confirm the presence of significant illness

- Complete blood count (CBC): Leukocytosis, leukopenia or eosinophilia (larva migrans).
- Erythrocyte sedimentation rate (ESR): Above 30 mm (first hour).
- C-reactive protein (CRP): Above 20 - 30 mg/liter.
- Chest x-ray: Pneumonic consolidation or pulmonary infiltrate.

Specific investigations to identify the causative disease

Initial investigations

- Blood culture (aerobic and anaerobic): May be repeated.
- Urine culture.
- Tuberculin test and culture of gastric washing.
- Blood film for malaria.
- Common serological tests: Typhoid (Widal), infectious mononucleosis (monospot), brucella.

When the above investigations are negative

- Specific blood culture for listeriosis, leptospirosis, tularemia.
- Specific serological tests for leptospirosis, tularemia, toxoplasmosis.
- Bone marrow examination (for leukemic blast cells) and culture (bacteria).
- Abdominal ultrasonography: For liver abscess, epinephric abscess.
- Echocardiography: In patients with preexisting cardiac disease (infective endocarditis).

When all above are negative

- Lymph node biopsy: May reveal lymphoma.
- Radioactive scanning: May reveal osteomyelitis.
- Total body CT scanning or MRI: May reveal hidden tumors.

- In 25% of cases, the cause remains unknown even after exhaustive investigations.

Blind empirical drug therapy should be generally avoided as it may mask the condition and makes the diagnosis more difficult. Exceptions to this rule are:

a) *Blind antibiotic therapy* in patients with the clinical diagnosis of septicemia but the organism could not be isolated.

b) *Blind antituberculous therapy* in sick patients with cachexia and weight loss and when the possibility of tuberculosis is strongly standing in spite of the negative laboratory investigations.

3. Skin Rashes (Exanthems)

Maculopapular rash	Vesicular rash
Common infections	**Common infections**
Scarlet fever	Chickenpox
Measles	Herpes simplex
German measles	Herpes zoster
Roseola infantum	**Skin and allergic conditions**
Erythema infectiosum	Papular urticaria
Enteroviral infections	Impetigo contagiosa
Skin and allergic conditions	Erythema multiforme
Sweat rash	
Drug rash	
Urticarial rash	
Papular urticaria	
Erythema muliforme	

Fever and skin rash is a common clinical presentation in pediatric practice. Maculopapular and vesicular rashes are the most common but the rash may be also:

- Purpuric: See short febrile illness.
- Bullous: Bullous impetigo, Stevens-Johnson syndrome.
- Nodular: Erythema nodosum, atypical mycobacteria and candida. Erythema nodosum occurs with viral, bacterial and fungal infections. It also occurs with systemic lupus erythematosus and inflammatory bowel diseases.

A) MACULOPAPULAR RASH

Causes of maculopapular rash can be clinically classified into 2 groups:

- **First group:** Skin rash is the essential characteristic feature and diagnosis cannot be made in absence of the rash. This group includes:

(a) Common infections: Scarlet fever, measles, German measles, roseola infantum, erythema infectiosum and enteroviral infections.

(b) Skin and allergic conditions: Sweat rash, drug rash, urticarial rash, papular urticaria and erythema multiforme.

- **Second group:** Skin rash is *not* the essential characteristic feature. It may or may not be present and diagnosis can be made in absence of the rash. This group includes:

(a) Infections: Typhoid fever, infectious mononucleosis and rickettsial diseases.

(b) Rheumatic diseases: Rheumatoid arthritis, systemic lupus erythematosis, dermatomyositis and Kawasaki disease.

Only the causes of the first group will be discussed here.

(a) Common infections

The diagnosis and differentiation between these infections depends on:

- Degree and duration of fever.
- Characters of the rash.
- Other characteristic clinical features.
- Complications, if present.

1. Scarlet fever: It is a bacterial disease caused by group A beta-hemolytic streptococci that release an erythrogenic toxin. It occurs after a short incubation period of 2 - 5 days.

- ***Fever:*** The disease starts acutely with fever, vomiting and abdominal pain. Temperature rises to 39.5 - 40.0°C on the second day and returns to normal over the next five days. With antibiotic therapy, it drops to normal after 24 hours of initiation of therapy.

- ***Rash:*** It appears on the *first or second day* and soon becomes generalized as a red punctate or finely papular rash (gooseflesh or sandpaper appearance). The face appears flushed with circumoral pallor. It remains for 3 - 7 days and fades with branny desquamation (see short Atlas in Pediatrics).

- ***Characteristic features:*** The most important 2 features are the presence of sore throat (pharyngitis and tonsillitis) and lingual changes. In early days, the tongue has a white coat with prominent papillae *"white strawberry tongue"*. After several days the white coat desquamates leaving a red tongue with prominent papillae *"red strawberry tongue"*.

- ***Complications:*** They may occur especially in those not receiving antibiotic therapy. *Early complications* are related to the spread of infection to other areas as sinuses (sinusitis), ears (otitis media) and lungs (bronchitis or pneumonia). *Late complications* may occur 2 - 3 weeks later, in form of autoimmune diseases as rheumatic fever or poststreptococcal glomerulonephritis.

2. Measles (Rubeola): It is a viral disease, which occurs after an incubation period of about 2 weeks. Infants below the age of 6 - 9 months are protected because of the transplacental acquired immunity from the mothers who have had measles or measles immunization.

- ***Fever:*** The disease starts with fever, which rises gradually during the first 4 days to reach 40.0°C with appearance of the rash, then after another 2 days it declines rapidly to normal (after the rash reaches the feet). The fever is associated with severe catarrhal manifestations (triad of rhinitis, conjunctivitis and cough). Cough is very important, as the diagnosis cannot be made in absence of cough.

- ***Rash:*** It appears on the *4th or 5th day*. It starts behind the ears and after 24 hours it covers the upper half of the body. After another 24 hours it reaches the thighs and feet. The rash characteristically reaches the feet while still in the face. It fades in the same order of distribution over the next 3 days (i.e. 3 days to appear and 3 days to fade).

• ***Characteristic features***: The most important pathognomonic feature of measles is the *koplik's spots*. They appear as white grains of sand surrounded by red areola and located on oral mucosa opposite to the lower molar teeth. They appear on the third day of illness (one day before the onset of rash), remain for one or 2 days and disappear with appearance of the rash (i.e. it is an early diagnostic sign).

• ***Complications:*** Pneumonia and encephalitis are the most serious complications. *Pneumonia* may be caused by the measles virus but more commonly it is caused by secondary bacterial infection. *Encephalitis* may accompany the illness (viral encephalitis), occurs 2 - 3 weeks later (allergic encephalitis) or occurs several years later (subacute sclerosing panencephalitis). *Black measles* characterized by a purpuric rash and hemorrhagic manifestations is uncommon.

• *Measles in vaccinated children* is usually milder in severity or atypical.

3. German measles (Rubella): It is a viral disease, which occurs after an incubation period of about 2 - 3 weeks.

• ***Fever:*** The disease starts with mild fever and lymphadenopathy. The fever remains only for 1 - 2 days and it may be absent (cold measles).

• ***Rash:*** It starts on the *first or second day* on the face and spreads rapidly to involve the trunk, then it extends rapidly to cover the whole body in 24 hours. The rash characteristically leaves the face while reaching the trunk and it clears completely by the third day (3 day measles). See short Atlas in Pediatrics.

• ***Characteristic features:*** The most important characteristic feature is the *lymphadenitis* of the occipital, post-auricular and posterior cervical groups.

• ***Complications*** are almost absent in children. German measles in pregnant women is serious to the developing fetus. Congenital rubella infection is associated with serious anomalies especially cataract and congenital heart disease.

4. Roseola infantum (Exanthem subitum): It is a viral disease of infants and young children, which occurs after an incubation period of one week.

• ***Fever:*** The disease starts with a sudden fever, which rises rapidly to 39.5 - 41.0C°. It remains high for 3 - 4 days without any localizing signs then it falls by crisis with appearance of the rash.

• ***Rash:*** It appears on the 4th day with the drop of temperature. It starts on the trunk and spreads rapidly to arms and neck with minimal face involvement. It fades very rapidly in 24 hours. The rash can be considered as a good sign because complete recovery will occur over the next 24 hours (see Short Atlas in Pediatrics).

• ***Characteristic features:*** The most characteristic feature is the sudden drop of temperature with appearance of the rash. Early diagnosis before appearance of the rash is difficult but the condition should be suspected in presence of high fever without localizing signs in late infancy.

• ***Complications:*** *Febrile convulsions* may occur with the sudden rise of temperature in susceptible infants.

5. Erythema infectiosum (Fifth disease): It is a viral disease, which occurs after an incubation period of 1 - 2 weeks.

- ***No fever:*** It is an afebrile disease.
- ***Rash:*** The disease starts with appearance of the rash. It appears suddenly on the face, giving the child a "slapped cheek appearance". After 24 hours, a second rash appears on the trunk and extensor surface of extremities. It remains for 1 - 2 weeks and fades with central clearing giving a characteristic lacy or reticular appearance. Periodic recurrence of the rash may occur with exercise, warm baths or emotional stress. The rash is commonly pruritic.
- ***Characteristic features:*** The most important characteristic features are the absence of fever and the presence of 2 rashes.
- ***Complications*** are rare. Arthritis, pneumonia or encephalitis may occur.

6. Enteroviral infections: Nonpolio enteroviruses (as coxsackieviruses and echoviruses) are a common cause of fever and rash especially in summer season. The rash may mimic any of the above exanthems or may be nonspecific. It may be also purpuric and closely resembles meningococcemia. The possibility of enteroviral infection should be considered when the picture does not fit with any of the above exantnems especially in summer season.

b) Skin and allergic conditions

1. Sweat rash (Miliaria rubra): It is a common inflammatory disease of the skin caused by mechanical obstruction of sweat ducts. It is particularly common in infants especially in hot weather (in summer season). The rash involves mainly the neck, trunk and diaper area but the limbs and face may be also affected. The lesion is usually *fine papular with intense erythema*. Vesiculation may occasionally occur (miliaria crystallina). The condition responds dramatically to cooling by regulation of environmental temperature and by removal of excessive clothing. A cool bath is often helpful in relieving pruritis. Topical agents are ineffective and may exacerbate the eruption (see Short Atlas in Pediatrics).

2. Drug rash: The possibility of drug rash should be considered in any patient receiving drugs especially penicillins or antipyretics. The distribution and the severity of the rash are variable and it usually lacks the special characters of the common exanthems. The rash disappears shortly after discontinuation of the responsible drug.

3. Urticarial rash: Although it is not a typical maculopapular rash, it is useful to be mentioned here to differentiate it from the above 2 conditions. The urticarial rash may be localized or generalized and it consists of a *circumscribed erythematous raised skin lesions (wheals)*. The individual lesion resolves within two days but new ones may continue to appear singly or in crops. The lesions are usually itchy and itching may be intense (see Short Atlas in Pediatrics).

Causes of urticarial rash

Ingestants	Ingestion of certain foods (as fish, banana, chocolates, nuts) or certain drugs (as penicillin, sulphonamides, aspirin).
Injectants	Injection of drugs (penicillin), serum or blood transfusion. Insect stings and bites may be also responsible.
Inhalants	Inhalation of pollens, danders or mites.
Contactants	Skin contact with drugs or chemicals.
Physical	Exposure to cold (cold urticaria), sun (solar urticaria) or exercise.
With diseases	SLE, Henoch-Schonlein vasculitis, lymphoma, urticaria pigmentosa.

4. Papular urticaria: It is a very common condition in children, which represents a delayed hypersensitivity reaction to insect bites. Fleas, ants and mosquitoes are the main responsible insects. The papular lesions may appear in large numbers and usually involve the extensor surfaces of extremities. The trunk may be also involved but the face and scalp are spared. The individual papule is about 2 - 5 mm in diameter and is surrounded by an erythematous area. Some papules, but not all, may vesiculate. The lesions are itchy and usually persist for more than 2 weeks (see Short Atlas in Pediatrics). Recurrences are common. The condition should not be confused with other papular lesions especially scabies. In ***scabies*** the intensely pruritic eruption involves the interdigital spaces, wrists, elbows, ankles, buttocks, umbilicus, groin and genitalia, and the papules are usually smaller in size than those of papular urticaria.

5. Erythema multiforme: It is a hypersensitivity reaction to a variety of causes as drugs, infections or exposure to toxic substances. The disease occurs in 2 forms:

a) Erythema multiforme minor: It is characterized by skin involvement only. The skin lesions are variable and multiple and may be *maculopapular, vesicular or urticarial*. The lesions appear in crops for up to 3 weeks and affect mainly the extensor surface of extremities with symmetrical distribution. Palms and soles may be also affected. The pathognomonic skin lesion *"iris or target lesion"* is formed of urticarial lesions where dusky centers are surrounded by darker rings. The skin lesions are *not itchy* and heal with hypo or hyperpigmentation but with no scarring (see Short Atlas in Pediatrics).

b) Erythema multiforme major (Stevens-Johnson syndrome): It s a severe serious form characterized by involvement of the skin and mucous membranes. The illness starts abruptly with fever, chills and weakness. The predominant lesions are *bullae* involving the skin, lips, mouth and conjunctiva. *cutaneous lesions* rupture and result in insignificant fluid losses. New lesions erupt for 1 - 4 weeks and healing occurs during the next 6 weeks. *Oral lesions* are painful and interfere with feeding. *Ocular lesions* including purulent conjunctivitis may result in serious complications. *Secondary bacterial infection* of the denuded skin may result in septicemia and death (see Short Atlas in Pediatrics).

3) VESICULAR RASH

(a) Common infections

Diagnosis and differentiation between these infections depend on:

- Degree and duration of fever.
- Characters of the rash.
- Other characteristic clinical features.
- Complications, if present.

1. Chickenpox (Varicella): It is a viral disease that occurs after an incubation period of 2 - 3 weeks. It may occur at any age including the neonates.

- ***Fever:*** The disease starts with mild fever and the skin rash. The fever remains only for 1 - 2 days. Occasionally, fever may be high and remains for a longer time.

- ***Rash:*** It appears first on the trunk and spreads to face and proximal parts of extremities *(centripetal distribution).* The rash appears in successive crops over 3 - 4 days. Each crop starts as a maculopapular, which rapidly vesiculates. Vesicles are oval teardrops surrounded by a red erythema. On the second day they change to pustules then crusts. So, at the peak of the disease the rash consists of crusts (earliest crop), pustules (next crop), vesicles and papules (latest crop)... i.e. the rash is *pleomorphic.* The rash is characteristically associated with itching *(pruritic).* The duration of illness from the papules of first crop to the crusts of last crop is one week (see Short Atlas in Pediatrics).

- ***Characteristic features:*** No other characteristic features apart from the fever and the pleomorphic vesicular rash.

- ***Complications:*** Although the disease runs a benign course in most cases, serious and even fatal complications may occur especially in young infants and immunologically deficient patients. *Secondary bacterial infection* of the skin lesions may occur due to scratching. *Hematological complications* as thrombocytopenia and purpura fulminans may also occur in infants (see short Atlas in Pediatrics). *Neurological complications* include encephalitis, Guillain Barre syndrome, facial nerve palsy and optic neuritis.

2. Herpex simplex: It is a viral disease that occurs after an incubation period of about one week. It may occur at any age including neonates.

- ***Fever:*** The disease starts with fever, which may reach 40.0°C or more and may remain as long as 10 days.

- ***Rash:*** It appears on the *second or third day.* It mainly affects the *mucocutaneous junctions* (the angles of the mouth or near genitalia) but it may be generalized. The rash starts as vesicles, which are characteristically *painful* and *uniform* (not pleomorphic). They change to pustules and crusts over a period of 10 days. *Recurrences* may occur.

- ***Characteristic features:*** The distribution of the rash is the most characteristic feature.

- ***Complications:*** Although the course is benign in most cases, a severe generalized form may occur in newborns, malnourished infants and immunodeficient patients and it may be fatal (see Short Atlas in Pediatrics).

3. Herpes zoster (Shingles): It is a viral disease that mostly occurs in adults. It is uncommon below the age of 10 years.

• ***Fever:*** The disease starts with fever and pain along the involved dermatome. Fever may remain along the course of illness (2 - 3 weeks).

• ***Rash:*** It appears *after few days* and is characteristically *unilateral* and confined to a dermatome or 2 adjacent ones. The most commonly involved areas are the trunk, face and scalp. It starts as groups of palpules, which rapidly vesiculate, then become pustular and dry over a period of 5 - 10 days. Successive crops appear for 1 - 4 days along the course of the nerve. The rash remains for 2 -3 weeks. It is characteristically accompanied with *pain and tenderness* along the involved dermatome (see Short Atlas in Pediatrics).

• ***Characteristic features:*** The unilateral distribution and the accompanied pain and tenderness are the most characteristic features.

• ***Complications:*** In children, the course is usually mild and the prognosis is generally good. Transient paralysis of the affected part is rare. Other complications as post-herpetic pain and keratitis are rare in children.

(b) Skin and allergic conditions

1. Papular urticaria: This common condition can be easily confused with early chickenpox. The main differences from chickenpox are:

- It affects mainly the extensor surface of extremities.
- Some papules, but not all, vesiculate and the vesicles cannot be easily broken as those of chickenpox.
- It is persistent for 2 weeks or more and recurrences are common due to repeated exposure to insect bites.

2. Impetigo contagiosa: It is a common skin infection caused by a group A beta hemolytic streptococci and occurs mainly in children during the hot summer season. The main sites of involvement are the exposed areas as the face, neck and limbs but lesions may appear anywhere in the body. It starts as erythematous macules that rapidly develop into thin-walled vesicles and pustules. The vesiculopastular lesions also rapidly develop into sticky raised crusts. Removal of the crusts leaves a moist red base with rapidly accumulating exudate. Although it is a self-limited disease, treatment with oral erythromycin or first generation cephalosporin is important for complete eradication of the infection. ***Bullous impetigo*** characterized by bullous lesions is caused by a staphylococcal infection (see Short Atlas in Pediatrics).

3. Erythema multiforme: When vesicular lesions predominate, the condition needs to be differentiated from other causes of vesicular rash. The multiplicity of lesions and the prolonged course help in differentiation (see maculopapular rash).

4. Parotid Swelling

Acute parotid swelling	Chronic parotid swelling
Epidemic parotitis (Mumps) Parotitis due to other viruses Bacterial (suppurative) parotitis Recurrent (allergic) parotitis Obstructive enlargement Strictures, calculi	Chronic parotitis Endemic parotitis Mikulicz disease Sarcoidosis Parotid tumors Benign, malignant

The normal parotid gland is not palpable. Epidemic parotitis (mumps) is by far the most common cause of parotid swelling, followed by infections with other viruses.

A parotid swelling occupies the parotid region over the angle of the mandible. It is continuous above and below the border of the mandible and it elevates the ear lobule and pushes it upwards and outwards. It may be acute or chronic, unilateral or bilateral and diffuse, localized or nodular swelling.

Parotid swellings should not be confused with other nearby swellings especially preauricular lymph nodes and cervical lymph nodes. These swellings lack the specific characters of the parotid swelling.

A) ACUTE PAROTID SWELLING

1. Epidemic parotitis (mumps): It is a viral disease, caused by myxovirus parotitis, which occurs after an incubation period of 2 - 3 weeks. The illness starts acutely with fever and swelling of one parotid gland. Swelling of the other parotid gland follows after 1-2 days. The swelling reaches its peak within 2 - 3 days and subsides slowly over 3-7 days. The swelling is painful and tender and better seen than felt because the edema of the skin and soft tissues usually extends and masks the limits of the swelling. It may be associated with edema and redness about the opening of Stensen's duct on oral mucosa. The parotid swelling may be accompanied with swelling of other salivary glands (submandibular and sublingual glands). In some cases, swelling of submandibular glands occurs without parotid swelling. Although the course is generally benign in most cases, serious complications may occur. *Meningoencephalitis* is the most common and it is manifested by vomiting, headache, irritability and neck rigidity. *Pancreatitis* may also occur and leads to acute abdominal pain and vomiting. *Orchitis* is rare before puberty. Diagnosis can be confirmed by the presence of elevated serum amylase level.

2. Parotitis due to other viruses: Coxsackie virus A or echovirus infection can produce parotitis, which can be only differentiated from mumps by specific laboratory tests. These infections are not common but may be considered when acute parotitis occurs in children who have had mumps.

3. Bacterial (suppurative) parotitis: It is most frequently seen in neonates and infants. Staphylococcus is the most common organism. The gland is tender and red, and significant systemic manifestations as high fever are usually present. In some cases, pus can be expressed from Stensen's duct.

4. Recurrent (allergic) parotitis: It is of unknown etiology but probably allergic in nature. It is characterized by recurrent episodes of parotid swelling. The enlargement is usually *unilateral*, associated with mild pain and lasts 1 - 2 weeks. The recurrences resolve at puberty.

5. Obstructive enlargement: *Strictures* of the duct may occur secondary to poor oral hygiene, dental or external trauma, recurrent infection or calculi. The swelling usually occurs suddenly during eating and is painful. Secondary infection is common. *Calculi* can rarely produce the same picture.

B) CHRONIC PAROTID SWELLING

1. Chronic parotitis: A history of repeated bilateral swellings is usually obtained. The enlargement of the glands is often bilateral and it is difficult to be distinguished from parotid tumours. Biopsy is important for differentiation.

2. Endemic parotitis: It is seen in children and adults of rural areas with bilharzial hepatosplenomegaly and hypoprotienemia. The parotid enlargement is usually *bilateral*, diffuse and painless.

3. Mikulicz disease: It is a disease of adult women but it may occur also in children. It causes *bilateral* painless swelling of the parotid glands simulating neoplasms. It may be associated with enlargement of the lacrimal glands (absence of tears).

4. Sarcoidosis: Swelling of the parotid gland occurs in less than 10% of cases of sarcoidosis. The swelling is firm, painless and nodular.

5. Parotid tumours: They are generally rare. *Hemangioma* is the commonest one in infancy. The swelling is soft and not tender and may become more intense during crying. *Lymphangioma* produces a more diffuse swelling. *Mixed parotid tumor* produces a firm painless mass. *Mucoepidermoid tumour* is the most common malignant parotid tumor. It presents as a firm, mobile mass in the parotid fascia. Other malignant tumors as lymphosarcoma are rare.

Biopsy is essential for accurate diagnosis of chronic parotid swelling.

5. Lymphadenopathy

Cervical lymphadenopathy	Generalized lymphadenopathy
Infections	**Infections**
Acute cervical lymphadenitis	Infectious mononucleosis
Chronic nonspecific lymphadenitis	Tuberculosis
Tuberculous lymphadenitis	Toxoplasmosis
Other causes	**Other causes**
Lymphoma	Lymphoma
Kawasaki disease	Leukemia
Sinus histiocytosis	Systemic lupus erythematosus

Before the age of 4 years, all superficial lymph nodes can be easily palpated. Lymph node enlargement is a quite common presentation, which mostly caused by infections. However in chronic enlargement, lymphoma should be considered. Lymphdenopathy can be regional or generalized

A) CERVICAL LYMPHADENOPATHY

It is an enlargement of the lymph nodes of the neck without any significant enlargement of other groups as axillary or inguinal lymph nodes.

(a) Infections

1. Acute cervical lymphadenitis: This common condition is caused by viral or bacterial infection of the cervical lymph nodes. ***Viral cervical adenitis*** is usually associated with viral upper respiratory tract infection. The enlargement is usually *bilateral* and the nodes are swollen and slightly tender. ***Bacterial cervical lymphadenitis*** usually accompanies bacterial infections of the oral cavity (as streptococcal pharyngitis) or other areas of head and neck. The enlargement can be *unilateral or bilateral* and the nodes are more severely swollen (3-6 cm in diameter), tender, warm and with erythema of the overlying skin. Suppuration and abscess formation may occasionally occur. The most common causative bacteria are staphylococcus aureus and group A streptococci. Anaerobic bacteria may be also responsible. ***Cat-scratch disease,*** following scratching of the skin by a cat or a dog, should be also considered. It produces *unilateral* enlargement and the nodes are often red, tender and quite large (8 - 10 cm in diameter). Suppuration occurs in 25% of cases and gradual slow recovery occurs over a period of 6- 8 weeks. The causative organism is a small pleomorphic gram-negative bacillus (Bartonella hensela). Diagnosis is mainly clinical but it can be confirmed by indirect immuno-fluorescent assay (IFA). If biopsy is taken, bacteria may be visualized by special stains. Bartonella DNA can be identified by polymerase chain reaction (PCR). Treatment with antibiotics is not clearly beneficial.

2. Chronic nonspecific lymphadenitis: It may occur chronic or frequently recurrent pharyngitis and tonsillitis. The enlarged nodes are firm, discrete, mobile and slightly tender. The enlargement is usual *bilateral* and the nodes are not large (less than 3 cm diameter). There are no other associated manifestations and the other groups are not involved.

3. Tuberculous lymphadenitis: Tuberculosis of cervical lymph nodes is a common presentation of tuberculosis. The enlargement is usually *bilateral* and the nodes are firm, discrete and not tender. In advanced cases, the nodes become very large (more than 6 cm in diameter) with matting and fluctuation. The anterior and posterior cervical lymph nodes are commonly affected. The condition may be associated with other manifestations as chronic cough and the other groups of lymph nodes may be also enlarged but to a lesser extent. Tuberculin test is usually positive ad chest x-ray may reveal an evidence of primary pulmonary tuberculosis. Total excision biopsy is essential for definite diagnosis. The condition should be differentiated from other infections especially cat scratch disease, tularemia, brucellosis and toxoplasmosis.

(b) Other causes

1. Lymphoma: Cervical lymphadenopathy is one of the main presentations of Hodgkin disease and non-Hodgkin lymphoma. The enlargement may be *unilateral or bilateral.* The enlarged nodes are firm, discrete, not tender with no regional inflammation to explain it. The condition may be associated with enlargement of other groups especially supraclavicular, axillary or inguinal lymph nodes. Nodal biopsy is essential for diagnosis and for identification of the pathological type. More than one nodal biopsy may be needed (see common malignancies).

2. Kawasaki disease (mucocutaneous lymph node syndrome): It is a disease of unknown etiology mainly affecting children below the age of 5 years. The illness starts abruptly with *high fever,* which remains for one to several weeks. The fever is associated with at least *4 of the following 5 conditions* (1) Bilateral mucopurulent conjunctival injection, (2) changes in the mucosa of oropharynx including dry erythematous fissured lips, strawberry tongue and pharyngeal injection, (3) edema, erythema and peeling of finger tips, (4) Skin rash which may be maculopapular or erythema multiforme but not vesicular, (5) Cervical lymphadenopathy which is nontender, may be large and unilateral or bilateral. *Cardiac involvement* in form of coronary vasculitis is the most important manifestation and it occurs in about 30% of cases. Manifestations of coronary vasculitis include coronary dilatation or aneurysm formation with signs of myocardial ischemia. Prognosis is generally good and most cases recover completely over several weeks.

3. Sinus histiocytosis with massive lymphadenopathy: It is a localized form of histiocytosis mostly seen in children of African origin. It presents with massive cervical lymphadenopathy, fever and leukocytosis. Mediastinal lymph nodes may be also massively enlarged. The condition is benign and gradual resolution occurs over several months Diagnosis is made by lymph node biopsy and demonstration of histiocytic changes. The condition should be a differentiated from other causes of cervical lympha-

...opathy with mediastinal lymph node enlargement especially lymphoma, T cell ...kemia and tuberculosis.

Causes of cervical and mediastinal lymphadenopathy

Tuberculosis Lymphoma T-cell leukemia Sinus histiocytosis	**Lymph node biopsy** is essential for diagnosis and differentiation

B) GENERALIZED LYMPHADENOPATHY

Generalized enlargement of all superficial lymph nodes (cervical, axillary and ...guinal groups) may accompany a long list of diseases. In most cases, generalized ...mphadenopathy is *not* the main presentation and diagnosis can be usually based on a ...ore specific presentation.

When generalized lymphadenopathy is main presentation, the following possibilities ...ould be considered:

(a) *Infections*

1. Infectious mononucleosis: Prolonged fever, pharyngitis and splenomegaly are usually present. Diagnosis depends on the presence of absolute lymphocytosis, atypical lymphocytes and serological evidence of Epstein-Barr virus (monospot test and Paul-Bunnel test). For more details of this common infection, see sore throat.

2. Tuberculosis: Prolonged fever, weight loss and/or chronic cough are usually present. Tuberculin test and lymph node biopsy are essential for diagnosis (see also weight loss and cachexia).

3. Toxoplasmosis: Prolonged fever and/or focal infections as pneumonia, pericarditis, encephalitis or polymyositis may be present. Diagnosis is made by demonstration of the characteristic histology of lymph node biopsy. Demonstration of *tachyzoites* in biopsy section or bone marrow aspirate and serological tests as *Sabin-Feldman dye test* is also very useful for diagnosis.

(b) *Other causes*

Lymphoma and leukemia should be also excluded. In rheumatic diseases as systemic lupus erythematosus, several other findings are usually present (see arthritis).

6. Weight Loss and Cachexia

Chronic infections	Rheumatic diseases	Malignancies
Chronic typhoid	Systemic lupus erythematosus	Leukemia
Chronic brucellosis		Lymphoma
Typhoidal tularemia		Neuroblastoma
Infectious mononucleosis		Malignant histiocytosis
Toxoplasmosis		
Tuberculosis		

When weight loss and cachexia are the main clinical presentation in a child, chronic infections, rheumatic diseases and malignancies should be considered. In all these conditions, ***nonspecific clinical findings*** as prolonged fever, Lymphadenopathy, hepatosplenomegaly and anemia may be present and ***nonspecific laboratory findings*** as leukocytosis, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be also present.

Precise diagnosis depends on ***specific laboratory findings***.

- ***Infections*** as typhoid fever, Brucellosis, tularemia, infectious mononucleosis and toxoplasmosis can be diagnosed by specific serological tests. Diagnosis of tuberculosis depends on the presence of strongly positive tuberculin test, possible nodal biopsy and culture of gastric wash for mycobacterium tuberculosis. Tuberculous bacilli DNA can be identified by polymerase chain reaction (PCR).
- ***systemic lupus erythematosus*** is diagnosed by a combination of clinical and laboratory findings (see arthritis).
- ***Malignancies*** as leukemia, lymphoma, neuroblastoma and malignant histiocytosis usually necessitate bone marrow examination (see common malignancies).

Tuberculosis should be always considered especially in low socioeconomic classes. History of vaccination against tuberculosis and family history of chronic cough or any other presentations suggesting tuberculosis are important.

Clinical presentations of tuberculosis

Unexplained prolonged fever.
Cervical or generalized lymphadenopathy.
Weight loss and cachexia.
Arthritis and/or back deformity (Pott's disease).
CNS: Tuberculous meningitis
Chest: Pulmonary tuberculosis (chronic cough or pleural effusion)
Heart: Constrictive pericarditis.
GIT: Chronic diarrhea (tuberculous enteritis) and/or ascites (tuberculous peritonitis).

7. Arthritis

Infections	Rheumatic diseases	Malignancies
Septic arthritis	Rheumatic fever	Leukemia
Osteomyelitis (with effusion)	Juvenile rheumatoid arthritis	Lymphoma
Toxic synovitis of the hip	Systemic lupus erythematosus	Neuroblastoma
Reactive arthritis	Ankylosing spondilitis	Malignant histiocytosis
Viral arthritis	Dermatomyositis	Rhabdomyosarcoma
Lyme disease	Henoch-Schonlein purpura	Osteogenic sarcoma
Tuberculous arthritis	Inflammatory bowel disease	Other bone tumors

Other causes of arthritis

Hematological conditions: Sickle cell anemia, hemophilia

Orthopedic conditions: trauma, avascular necrosis, slipped capital femoral epiphysis

Genetic disorders: Lipid storage disease as Farber disease

Arthritis (inflammation of synovial membranes of a joint or joints) is a common presentation in pediatric practice. Although rheumatic diseases are the most common, infections and malignancies should be always considered.

- How to diagnose arthritis?
- Is it acute (transient) or chronic?
- Is it monoarticular, pauciarticular or polyarticular?
- What are the associated clinical manifestations?
- What is the cause?

1. *How to diagnose arthritis?*

In classic cases, the inflamed joint is swollen, red, hot, tender, and painful with stiffness and limitation of movements. Swelling of the joint is the most reliable sign of arthritis. In absence of a swelling, two of the following 4 criteria are sufficient for diagnosis (1) pain and tenderness, (2) redness, (3) hotness (4) Stiffness and limitation of movements. It is important to remember that pain in a joint (arthralgia) without any other manifestations is not enough to diagnose arthritis.

Arthritis should not be confused with ***other causes of leg pain*** as:

- *Muscle pain* as in myositis. The pain and tenderness are limited to muscles.
- *Bone pain* as in trauma, fractures, osteomyelitis and malignancies.
- *Growing pains:* It is a very common condition of uncertain etiology most commonly seen in children between 3-6 years. It is characterized by intermittent annoying pain or ache. The pain is always bilateral usually localized in the muscles of the thighs and legs

with no or minimal joint pains. It usually occurs in the evening and even during sleep and usually disappears in the morning. The pain is not related to exercise and does not disappear after rest, which is an important differentiating point from pain of fatigue. The pain is not associated with tenderness, erythema, swelling or limping and there are no other clinical or laboratory findings. Diagnosis should be only made after exclusion of organic causes of leg pains. Reassurance of the parents is important.

2. Is it acute or chronic?

Acute (or transient) arthritis is an arthritis, which lasts for less than 6 weeks. Acute infections, rheumatic fever, Henoch-Schonlein purpura and acute leukemia are the main causes. **Chronic arthritis** (arthritis with duration more than 6 weeks) suggests juvenile rheumatoid arthritis as a first possibility. Other rheumatic diseases and chronic infections should be also considered.

3. Is it monoarticular, pauciarticular or polyarticular?

In every case of arthritis, examination of all joints is essential. Examination should include ***large joints*** (shoulders, elbows, wrists, hips, knees, ankles and sacroiliac joints) and ***small joints*** (hands, feet, neck and temperomandibular joints).

- **Monoarticular arthritis** is an affection of only ***one*** large joint. Septic arthritis, osteomyelitis with sympathetic effusion, toxic synovitis of the hip, trauma to a joint and slipped capital femoral epiphysis are the main causes. Diagnosis of rheumatic fever should never be made in case of monoarticular or non-migrating arthritis.
- **Pauciarticular (oligoarticular) arthritis** is an affection of ***few*** large joints (less than 5) with no small joint affection. Reactive arthritis, viral arthritis, pauciarticular juvenile rheumatoid arthritis and acute leukemia are the main causes.
- **Polyarticular arthritis** is an affection of ***many*** large joints (5 or more) with or without small joint affection. Polyarticular rheumatoid arthritis, tuberculous arthritis and malignancies are the main causes

4. What are the associated clinical manifestations?

Detailed history and thorough complete examination are essential for precise diagnosis. History-taking should include history of trauma, fever, acute or chronic diarrhea and bleeding tendency and examination should include all systems with special emphasis on cardiac involvement.

5. What is the cause?

Although some investigations are usually required for accurate diagnosis, it should be emphasized that the diagnosis of juvenile rheomatoid arthritis and systemic lupus erythematosus is mainly based on clinical findings.

Diagnostic significance of associated clinical signs in arthritis

High fever and toxemia: Septic arthritis, osteomyelitis with sympathetic effusion.
Acute diarrhea: Reactive arthritis.
Chronic diarrhea: Inflammatory bowel diseases (Crohn's disease, ulcerative colitis).
Purpura: Henoch-Schonlein purpura, acute leukemia.
Malar butterfly rash: Systemic lupus erythematosus.
Cardiac involvement: Rheumatic diseases.
Hepatosplenomegaly: Rheumatic diseases or malignancies.

Possible investigations in arthritis

CBC, ESR and CRP: In ALL cases.
Blood culture and culture of aspirated joint fluid: In septic arthritis.
Antistreptolysin O titer (ASO): In suspected rheumatic fever.
Antinuclear antibodies (ANA) and rheumatoid factor (RF): In rheumatoid arthritis.
LE cells, ANA and antibodies to double stranded DNA: In systemic upus erythematosus.
HLA B27: In suspected ankylosing spondilitis (positive in 95°/s of cases).
Serum transaminases and creatine kinase: In suspected dermatomyositis.
Bone marrow biopsy and/or joint biopsy: In suspected malignancies.

A) INFECTIONS

1. Septic arthritis: Bacterial infection of a joint occurs secondary to septicemia, adjacent osteomyelitis or penetrating trauma. The main causative organisms are staphylococcus aureus and hemophilus influenza. It is the most important cause of *acute monoarticular arthritis*. The main involved joints are the knee (40%), hip (20%), ankle (15%), wrist (5%) and shoulder (5%). The affected joint is swollen, hot, red, very painful, tender with limitation of movement. Signs and symptoms of a septic hip in an infant may be limited to limp or a fixed flexed hip. High fever and toxemia are usually evident but fever may be occasionally absent. Leukocytosis, elevated ESR and CRP are usually present. Blood culture is positive in 50% of cases. Definite diagnosis depends on gram-stain and culture of aspirated joint fluid.

2. Osteomyelitis with sympathetic joint effusion: It is a sterile joint effusion in the joint adjacent to osteomyelitis of a long bone. The condition can be confused with septic arthritis because of the presence of *high fever and monoarticular arthritis*. Leg pain, focal tenderness over the affected bone and absence of redness and hotness of the affected joint help in clinical differentiation. Radionuclide scanning of the bone is helpful for early diagnosis. Skeletal changes in x-ray may take 1-2 weeks to appear.

3. Toxic synovitis of the hip: It is a common condition of uncertain etiology mostly seen in children between 2 - 8 years. It is the commonest cause of *unilateral hip pain and limping* in children. Pain is not severe and systemic manifestations as high fever

or toxemia are characteristically absent. The condition is self-limited and complete recovery usually occurs in 4 - 7 days. The condition should be differentiated from other causes of ***unilateral painful hip*** especially septic arthritis, osteomyelitis, slipped capital femoral epiphysis (following car accidents) and Perthes disease (chronic painful hip).

4. Reactive arthritis: It is a self-limited *transient pauciarticular arthritis* that occurs in older children as a reaction to bacterial gastroenteritis. Associated acute diarrhea due to salmonella, shigella, compylobacter or yersinia infection is usually present. Diagnosis depends on positive stool culture.

5. Viral arthritis: It is a self-limited *transient pauciarticular or polyarticular arthritis* that may accompany several viral infections. The arthritis usually occurs after the onset of viral illness except in hepatitis B where arthritis may antedate the onset of jaundice. Involvement of the small joints of the hands is common. The condition usually subsides over a few weeks.

6. Lyme disease: It is a multisystem spirochetal disease caused by borrelia burgdorferi. It is characterized by skin, neurologic and joint manifestations. Joint manifestations are usually *pauciarticular, episodic and recurrent.* Skin manifestations usually occur at the site of tick bite (erythema chronicum migrans). Diagnosis is made serologically by demonstrating antibodies against borrelia burgdorferi.

7. Tuberculous arthritis: Although uncommon, it should be considered in cases of chronic arthritis. It may be *monoarticular* affecting the knee, wrist or hip or it may affect *interphalangeal and metacarpal joints.* Other causes of chronic arthritis of the small joints of the hands especially sickle cell anemia should be considered Synovial biopsy and synovial fluid culture for acid fast bacilli are important for diagnosis

B) RHEUMATIC DISEASES

1. Rheumatic fever: Arthritis occurs in 75% of cases of rheumatic fever. It is *polyarticular,* affecting *large joints* (as knees, ankles, elbows and wrists), *transient* (less than one week in the affected joint) and *migratory* (leaves the joint without destruction to affect other joints). The inflamed joint is usually swollen, red, hot with tenderness and limitation of movements. The diagnosis of rheumatic arthritis should never be made in monoarticular or nonmigratory arthritis. To diagnose rheumatic fever, another major criterion (as carditis) or 2 minor criteria (fever and acute phase reactants) should be present in addition to an evidence of recent streptococcal infection (see rheumatic fever).

2. Juvenile rheumatoid arthritis (JRA): It is the commonest and main cause of chronic arthritis in children. Diagnosis of JRA is *clinical* and depends on the presence of chronic arthritis more than 6 weeks with exclusion of other causes of chronic arthritis. The onset may be fulminant or gradual. According to the onset in the first 6 months of illness, there are 5 subgroups:

a) Pauciarticular type I: It is the most common subgroup (40% of cases). The onset is in *early childhood* and it mainly affects females (80%). Only few large joints are affected (mainly knees and ankles) and *chronic iridocyclitis* occurs in 30% of cases. Antinuclear antibodies are positive in 90% of cases and prognosis is generally good.

c) *Pauciarticular type II:* It occurs in 10% of cases. The onset is in *late childhood* and it mainly affects *males* (90%). Only few large joints are affected (less than 5) and *sacroiliitis* is common. Antinuclear antibodies are negative but HLA B27 is positive. Prognosis is generally good.

d) *Polyarticular-Rheumatoid factor negative:* It is the second most common subgroup (25% of cases). It occurs *throughout childhood* mainly in *females* (90%). It affects small and large joints (more than 5 and up to 20 or more). Antinuclear antibodies are positive in 25% of cases but rheumatoid factor is negative. Prognosis is generally good.

e) *Polyarticular-Rheumatoid factor positive:* It occurs in 10% of cases. The onset is in *late childhood* (above the age 8 years) and it mainly affects *females* (80%). Arthritis is severe and prognosis is worse (50% only cure rate). Antinuclear antibodies are positive in 75% of cases and rheumatoid factor is positive.

f) *Systemic onset disease:* It occurs in 15% of cases. It occurs *throughout childhood* and both males and females are equally affected. It is a polyarticular disease (affecting small and large joints) with *prominent systemic manifestations* (intermittent fever, maculo-papular rash, hepatosplenomegaly lymphadenopathy and myocarditis or pericarditis but not endocarditis). Both antinuclear antibodies and rheumatoid factor are negative. The ultimate cure rate is about 75%.

Important remarks in juvenile rheumatoid arthritis (JRA)

- Diagnosis of JRA is clinical and not laboratory (persistent arthritis for more than 6 weeks).
- There are no diagnostic laboratory tests.
- Up to 80% of cases occur in females.
- Early-onset disease has a better prognosis than the late-onset disease.
- With early-onset disease (below 8 years), rheumatoid factor is always negative.
- With late-onset disease, positive rheumatoid factor is a bad prognostic sign.

3. Systemic lupus erythematosus (SLE): It is a disease of multi-system involvement mainly affecting females above the age of 8 years. Although arthritis is a common finding, it is usually transient, not severe and not the main dominating feature. It is important to remember that diagnosis of SLE is mainly ***clinical*** and it depends on multi-system affection. Laboratory confirmation is important but most findings are not specific for SLE. It is also important to remember that the clinical manifestations of SLE *do not appear simultaneously* but may appear serially over several months or years (see below). Spontaneous exacerbations and remissions are common. Prognosis is generally bad.

4. Ankylosing spondilitis: It is a disease that affects males above the age of 8 years and is characterized by persistent pain and stiffness in the back with or without arthritis. The main characteristic feature is the involvement of sacroiliac and lumbodorsal joints. Arthritis is present in half the patients and it is usually pauciarticular involving few large joints of the lower limbs. HLA B27 is positive in 95% of cases.

Clinical and laboratory findings of systemic lupus erythematosus

Clinical manifestations of multisystem involvement

Fever, weight loss and cachexia.
Cutaneous manifestations: Malar butterfly rash is the commonest. Diskoid rash is unusual.
Hematological manifestations: Anemia and purpura.
Arthritis: Transient, not severe (non-erosive).
Nephritis: In most cases. Persistent proteinuria (above 0.5 gm/day) or cellular casts.
Polyserositis: Pleurisy, pericarditis and peritonitis.
Pancarditis: Endocarditis, myocarditis, pericarditis.
Hepatosplenomegaly and generalized lymphadenopathy.
Neurological disease: Personality changes, seizures, peripheral neuritis.
Ocular manifestations: Episcleritis and iritis.

Laboratory findings

Antinuclear antibodies (ANA): are positive in all cases (not specific to SLE).
LE cell preparation is positive in severe active disease.
Anti-DNA antibodies are positive in severe active disease.
Immune pancytopenia: Hemolytic anemia, positive Coomb's test, leukopenia, thrombocytopenia.
Low serum complement in patients with active nephritis.

Criteria for diagnosis of systemic lupus erythematosus

1. Malar rash.
2. Discoid-lupus rash.
3. Photosensitivity.
4. Oral or mucocutaneous ulcerations.
5. Non-erosive arthritis.
6. Nephritis (proteinuria >0.5gm/day, cellular casts).
7. Pleuritis or pericarditis.
8. Encephalopathy (seizures, psychosis).
9. Cytopenia.
10. Positive antinuclear antibodies test.
11. Positive immunoserology: Antibodies to double-stranded DNA (ds-DNA).

Four or more of the above eleven criteria (present serially or simultaneously during a period of observation) are enough to diagnose SLE.

5. Dermatomyositis: It is a multisystem disease characterized by a slowly developing muscle lesion, cutaneous lesions and may be other manifestations as arthritis, hepatosplenomegaly and lymphadenopathy. ***Myositis*** is manifested by weak, tender and indurated muscles mostly of the proximal groups. The ***skin*** over the involved limbs is usually thickened, tight and may be adherent to the underlying structures. A dusky erythema may cover the upper trunk and proximal extremities. The pathognomonic skin rash is a faint malar rash with violaceous discoloration of eyelids *(heliotrope eye lids)*. Diagnosis is confirmed by the elevated serum transaminases and creatine kinase.

6. Henoch-Schonlein purpura: It is a vasculitis syndrome characterized by nonthrombocytopenic purpura, arthritis, abdominal pain and nephritis. ***Characteristic skin lesion*** is a purpuric rash involving mainly the back of lower limbs and buttocks but it may extend to involve the trunk and upper limbs. ***Arthritis*** occurs in two thirds of cases, affecting few large joints and remains for only few days. ***Gastrointestinal manifestations*** occur in 50% of cases. Colicky abdominal pain is the main feature and it may be associated with gastrointestinal hemorrhage (bleeding per rectum and may be hematemesis). ***Nephritis*** occurs in one third of cases and it may appear during the acute stage or few weeks after recovery. It is usually not severe, only manifesting with hematuria with or without casts and proteinuria. It usually subsides completely over few weeks but chronic renal disease may occur. ***Neurological manifestations*** as convulsions, coma and paralysis are rare but serious findings. Prognosis is generally excellent and most cases recover completely over few days or few weeks (see also purpura and Short Atlas in Pediatrics).

7. Inflammatory bowel diseases: The possibility of inflammatory bowel diseases (Chron's disease and ulcerative colitis) should be considered in cases of unexplained arthritis especially when associated with weight loss, unexplained fever, anemia, mucosal ulcers and erythema nodosum. Arthritis may antedate the onset of bowel symptoms by months or years (see chronic diarrhea).

C) MALIGNANCIES

Malignancies, especially ***acute leukemia, lymphoma and neuroblastoma***, should be considered in every case of arthritis with severe joint pain especially when it is associated with bone pains. Arthritis is usually persistent and not responding to therapy with salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs). Anemia, purpura, lymphadenopathy or hepatosplenomegaly may be also present. Bone marrow biopsy and/or joint biopsy are essential for diagnosis (see common malignancies).

5

Neurology

- Neurological Examination

1. Comatose Child.
2. Convulsions.
3. CNS Infections.
4. Acute Paralysis.
5. Floppy Infant.
6. Spastic Infant.
7. Progressive Motor Weakness.
8. Movement Disorders.
9. Neurocutaneous syndromes.

Neurological Examination

Quick examination to detect critical conditions
Level of consciousness (LOC)
Look for: Convulsions
Features of increased intracranial pressure
Features of lateralization
Features of meningeal irritation

Detailed examination
Mentality
Head examination: Head size, anterior fontanel, cranial nerves
Motor examination: Posture or gait, movement disorders, muscles, reflexes
Sensory examination: Superficial and deep sensations
Autonomic examination

A) QUICK EXAMINATION

Evaluation of the **level of consciousness (LOC)** should always be the first step in neurological examination. A normal infant or a child is conscious, alert and responsive. He responds to physical stimulation by crying or withdrawal movements.

With suspected disturbed consciousness, *a trial to arouse the patient* by (1) loud voice, (2) touch, (3) painful stimuli should be made. Disturbed consciousness can be graded as lethargy, confusion and coma. In this case, *neurological examination* should be directed for detection of convulsions, features of increased intracranial pressure, features of lateralization and features of meningeal irritation. Eye examination especially for cranial nerve reflexes is extremely important (see comatose child).

B) DETAILED EXAMINATION

1. Mentality: Mental development should be evaluated by observing the social development (in infancy) and assessment of speech development (in early childhood). In older children, school achievement or simple mathematical questions are helpful in evaluation of mental development (see mental retardation).

2. Head examination: From the neurological point of view, head examination should include the following

a) Head size: Measurement of head circumference is important especially in infants and young children. Abnormalities include small head and large head. Serial measurements may reveal that the head is exceeding its percentile (see growth and development and hydrocephalus).

b) Anterior fontanel: Bulging fontanel is reliable sign of increased intracranial pressure. It may be *acute* indicating brain edema as in comatose patients or it may be *chronic* without altered consciousness, as in case of hydrocephalus or brain tumors.

c) ***Cranial nerves:*** Examination of cranial nerves in infants and children needs some experience and patience especially in uncooperative patients

- *I (smell):* It is very difficult to be evaluated in infants. Transient loss occurs with rhinitis. Generally it is the least important.
- *II (vision):* Evaluation of vision is important. In young infants, optic blink in response to bright light indicates a normal vision.
- *III, IV, VI (eye movements):* In infants, it can be assessed by following a moving toy or moving light.
- *V (facial sensations):* Ophthalmic, maxillary and mandibular divisions can be assessed by observing the response to touch or painful stimuli.
- *VII (facial movements):* Eye closure and mouth movements during crying or smiling are the representatives of the upper and lower parts of the face.
- *VIII (hearing):* Can be assessed by observing the response to noise or speech.
- *IX, X (voice and swallowing):* Normal swallowing and loud crying indicate normal bulbar nerves. In bulbar palsy, weak cry, weak cough, nasal tone, nasal regurgitation, choking and aspiration are usually evident.
- *XI (neck and shoulder movements):* By observing a head turn to a side.
- *XII (tongue movements):* In unilateral paralysis, the tongue is deviated to the affected side (see hemiplegia).

Examination of cranial nerves in comatose patients depends on cranial nerve reflexes. Evaluation of brainstem function by brainstem reflexes is very important to identify the level of dysfunction (see comatose child).

Brainstem reflexes in comatose child and their significance

Pupillary light reflex: It tests cranial nerves 2 and 3 (Midbrain reflex).
Corneal reflex: It tests cranial nerves 5 and 7 (Pontine reflex).
Oculocephalic reflex: It tests cranial nerves 3, 4, 6 and 8 (Midbrain and pontine reflex).
Oculovestibular reflex: It tests cranial nerves 3, 4, 6 and 8 (Midbrain and pontine reflex).
Cough and gag reflex: They test cranial nerves 9 and 10 (Medullary reflex).

3. Motor examination: It should include the following 4 steps:

a) ***Posture or gait:*** In newborns and young infants, posture of flexion of 4 limbs indicates a normal motor system. Abnormalities in posture include *frog-leg position* of floppy infants and *scissoring of lower limbs* of spastic infants. In walking children, the gait should be observed for abnormalities (see below).

b) ***Movement disorders:*** They include *ataxia* (incoordination of movements) and abnormal *involuntary movements* (as chorea, athetosis, dystonia, tics and tremors).

Types of abnormal gait

Spastic gait

Circumduction hemiplegic gait: With spastic hemiplegia.
Toe walking paraplegic gait: With spastic paraplegia as in transverse myelitis.
Scissoring diplegic gait: With spastic cerebral palsy.

High steppage gait

With peripheral neuritis as in Guillain Barre syndrome.

Waddling gait

With weak hip muscles as in muscular dystrophies, achondroplasia, congenital hip dislocation.

Ataxic or drunken gait

With ataxia. It is a dancing unsteady gait with movements in any direction.

Limping gait (measurement of the length and circumference of both limbs is essential)

With unequal limbs: In hemihypertrophy, hemiatrophv or unilateral shortening as in monoplegia and in poliomyelitis.
With equal limbs: Nonpainful gait (hemiplegia or monoplegia).
Painful or antalgic gait (trauma, fracture, osteomyeliyis, arthritis, malignancy).

Hysterical gait

Changeable bizzare gait, which does not conform to any abnormal gait

b) Movement disorders: They include *ataxia* (incoordination of movements) and abnormal *involuntary movements* (as chorea, athetosis, dystonia, tics and tremors)

c) Muscles: It includes muscle bulk, muscle power and muscle tone.

- *Muscle bulk:* Wasting of muscles occurs in longstanding paralysis an in neglected poliomyelitis. Pseudohypertrophy of calf muscles occurs in Duchenne muscular dystrophy.

- *Muscle power:* It is assessed by observing the active movements and the ability to perform motor functions. Motor weakness (inability to perform motor function) is a common presentation in pediatric practice (see neurological presentations).

- *Muscle tone:* It is assessed by testing the resistance to passive movements. Abnormalities include hypotonia (flaccidity) and hypertonia (spasticity). Hypotonia may be present at birth (floppy infant), occurs acutely (acute paralysis) or gradually (gradual motor weakness).

d) Reflexes: Examination should include deep and superficial reflexes:

- *Tendon reflexes:* They include biceps and triceps reflexes in upper limbs and knee and ankle reflexes in lower limbs. Hyporeflexia is usually associated with hypotonia and hyper-reflexia with hypertonia. An exception is the hypotonia of brain origin which is usually associated with hyper-reflexia (see floppy infant).

- *Planter reflex (Babiniski sign):* Normally, scratching along the outer border of the foot by a blunt instrument (as a key) results in planter flexion of the big toe. Dorsiflexion of the big toe (after infancy) with fanning of other toes indicates a pyramidal lesion.

- *Ankle clonus*: Normally it is absent. It may be present in case of severe spasticity as in spastic cerebral palsy. It is elicited by sudden dorsiflexion of the foot while the knee is flexed. In positive response, repeated dorsiflexion-planter flexion movements occur.
- *Superficial reflexes* as abdominal reflexes are mainly important in case of paraplegia with sensory level as in transverse myelitis (see acute paralysis).

4. Sensory examination: Evaluation of sensations is difficult in infants and young children. Superficial sensory losses of relevance are:

- *Sensory level on the trunk* as in spinal cord lesions (transverse myelitis and spinal cord compression).
- *Glove and stocking* as in some cases of polyneuritis.

5. Autonomic examination: The most important autonomic disturbances are those accompanying spinal cord lesions (urinary retention and stool incontinence).

Clinical presentations of neurological diseases

Life-threatening presentations (neurological emergencies)
- Altered consciousness (coma)
- Convulsions (acute or recurrent)
- Acute increased intracranial pressure
- Meningeal irritation

Neurological disorders of growth and development (see growth and development)
- Small or large head
- Delayed motor development
- Mental retardation

Motor weakness
- Floppy infant
- Spastic infant
- Acute paralysis
- Gradual motor weakness

Movement disorders
- Incoordination of movements (ataxia)
- Involuntary movements (chorea, other movements)

Abnormal gait

Headache
- Vascular headache (migraine)
- Chronic increased intracranial pressure (see brain tumors)
    - Brain tumors
    - Pseudotumor cerebri

1. Comatose Child

Primary brain lesions (Direct brain lesion)	Secondary brain lesion (Encephalopathy)
CNS infections Meningitis Encephalitis Brain abscess Cortical thrombophlebitis Cerebral malaria Severe septicemia (toxins) **Intracranial hemorrhage** Traumatic head injury Nontraumatic causes Hemophilia, DIC ITP Sickle cell anemia Polycythemia Ruptured aneurysm Arteriovenous malformations **Postepiteptic (post-ictal) coma** Status epilepticus Following prolonged fits **Advanced brain tumor**	**Hypoxic encephalopathy** **Hypoxic hypoxic encephalopathy** Severe airway obstruction Severe respiratory failure Post-cardiopulmonary arrest **Hypoxic ischemic encephalopathy** Advanced shock (any cause) **Hypoxic anemic encephalopathy** Severe blood loss Severe acute hemolysis **Endogenous encephalopathy** **Acute organ failure** Acute renal failure Acute hepatic failure Diabetic ketoacidosis, hypoglycemia **Water and electrolyte disturbance** Water intoxication or dehydration Severe acidosis of alkalosis Hypo or hyper (Na, Ca, Mg) **Errors of metabolism** Organic acidemias Hyperammonemia **Exogenous encephalopathy (Poisoning)** Drug intoxication Environmental toxins

Coma is a state of prolonged unconsciousness in which the patient cannot be aroused (awakened) even with painful stimuli. It is a serious life threatening condition which necessitates urgent diagnostic and therapeutic measures to preserve life.

What is consciousness and where is it?

Consciousness is a state of self-awareness of several widely distributed functions as motor activity, sensations, vision, hearing, speech, memory and behavior. So, consciousness is awareness of all these functions

Consciousness depends on a continuous interaction between cerebral cortex and upper brainstem. In ***cerebral cortex***, consciousness is present *everywhere* (right and left, front and back). So, any cortical lesion that impair consciousness should be bilateral and diffuse affecting all, or almost all, cortical functions. Focal lesions in one hemisphere can cause severe neurological defect but it will not impair consciousness. In ***brainstem***,

consciousness is present in the ascending reticular activating system, which is located in *midbrain and upper two-thirds of pons*. So, any focal brainstem lesion affecting midbrain and upper pons can destroy the ascending reticular activating system and impair consciousness. To summarize, coma results from one of 2 conditions:

1. Bilateral diffuse cortical lesion impairing all cortical functions.
2. Focal small brainstem lesion in midbrain and upper pons.

- What is the level of consciousness?
- What is the level of dysfunction? Is it cortical or brainstem?
- What are the associated neurological signs?
- What are the associated physical signs?
- What is the cause?

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1. *What is the level of consciousness?*

Assessment of the level of consciousness is made by trying to arouse (awaken) the patient by sequential sensory stimuli (to voice, to touch, to pain) and observing the response. Painful stimuli can be made by supraorbital pressure, vigorous rubbing of the sternum or pressure on fingernails and toenails by a blunt object as a pencil.

There are 2 systems of assessment: the staging system and the scoring system. ***Staging system*** is simple and can be used by all physicians and nurses. ***Scoring system*** is more accurate especially in follow-up but it has several disadvantages.

Staging system of the level of consciousness

I. **Fully conscious and alert:** This is the normal consciousness.
II. **Lethargy:** Conscious but looks sleepy or somnolent with slow reactions.
III. **Confusion:** Conscious but with disorientation of the surroundings. Disturbed memory.
IV. **Unconsciousness (coma):** It is divided into 4 stages:
   1. Stupor: Can be aroused briefly (less than a minute), then becomes unconscious again.
   2. Light coma: Cannot be aroused. He responds to painful stimuli by:
      (a) Flexion withdrawal movements and moaning or
      (b) Decorticate extension (flexion of upper limbs and extension of lower limbs) or
      (c) Decerebrate extension (extension of the 4 limbs).
   3. Deep coma: Cannot be aroused. No response to painful stimuli. Breathing spontaneously.
   4. Deep coma with apnea: If not ventilated, brain death occurs in 4 minutes.

Brain death: 1) Deep coma (no response to painful stimuli).
2) Apnea (ventilator dependent, no respiration for 5 minutes ventilator off).
3) Absent eye brain stem reflexes (dilated fixed pupils, absent oculocephalic reflex)
4) No hypothermia, hypotension or CNS depressant drugs.
5) Persistent findings throughout the period of observation (12 to 24 hours).

Modified Glasgow coma score for children

Activity	Best response	Score
Eye opening	Spontaneous or to speech	4
	To load voice or touch	3
	To pain	2
	No response	1
Verbal response	Oriented and appropriate	5
	Words or irritable crying	4
	Cries to pain	3
	Moans to pain	2
	No response	1
Motor response	Spontaneous	6
	Flexion withdrawal to touch	5
	Flexion withdrawal to pain	4
	Decorticate extension to pain	3
	Decerebrate extension to pain	2
	No response (flaccidity)	1

Total score is 15 (4+5+6). Score below 8 indicates severe neurological injury.
Inability to assess any parameter will make it impossible to count he score:
* Eye opening cannot be assessed if the eyes are swollen and closed (trauma).
* Verbal response cannot be assessed in intubated and ventilated patients.

Modified Morray coma score for children

Activity	Best response	Score
Motor response (cortical function)	Spontaneous	6
	Flexion withdrawal to touch	5
	Flexion withdrawal to pain	4
	Decorticate extension to pain	3
	Decerebrate extension to pain	2
	No response (flaccidity)	1
Brainstem reflexes (brainstem function)	All normal	4
- Pupillary reflex	Some absent or diminished	3
- Corneal reflex	All absent but breathing	2
- Oculocephalic reflex	All absent and apneic	1
- Cough/gag reflex		

Total score is 10 (6+4). It tests cortical and brain stem functions separately.
Can be used in intubated and mechanically ventilated patients.
Eye reflexes and respiration are included in the score.

2. What is the level of dysfunction?

The level of dysfunction (cortical or brainstem) can be assessed by:

1. Motor response to painful stimuli (the 4 limbs should be tested).
2. Brainstem reflexes (both sides should be compared). It is the most important.
3. Respiratory pattern.

Level of dysfunction in comatose patient

Level	Motor response	Pupils	Respiratory pattern
Cortex	Flexion withdrawal	Small reactive	Normal or Cheyne-Stokes
Thalamus	Decorticab extension	Small reactive	Normal or Cheyne-Stokes
Midbrain	Decerebrate extension	Midposition, fixed	Neurogenic hyperventilation
Pons	No response	Pinpoint	Normal or apneustic
Medulla	No response	Small, reactive	Ataxic (irregular) breathing

MOTOR RESPONSE

1. **Flexion withdrawal** is a good prognostic sign as it indicates mild to moderate diffuse cortical lesion especially when associated with normal pupils and respiration.
2. **Spastic decorticate extension** (arms flexed against the chest and limbs extended) indicates a severe diffuse cortical and thalamic lesion.
3. **Spastic decerebrate extension** (four limbs are extended) indicates a midbrain dysfunction especially when associated with midposition fixed pupils.
4. **Flaccidity with no response to painful stimuli** is a bad prognostic sign as it indicates either severe cortical lesion or low brainstem lesion (pons or medulla). The prognosis is worst with ataxic breathing because the next step is apnea and brain death.
5. **Steady deterioration** with change of the motor response from flexion withdrawal to extension indicates a central transtentorial herniation due to supratentorial structural disease. In this case the level of dysfunction change from cortical to thalamic, midbrain, pons then medulla (rostral-to-caudal deterioration or deterioration from above downwards). Urgent CT and urgent measures to reduce the increased intracranial pressure are essential.
6. **Asymmetric response:** Motor response can be symmetric (diffuse lesion), asymmetric (focal lesion). Asymmetric response (whether cortical or brainstem) is an urgent indication to CT scan of the head.

BRAINSTEM REFLEXES

1. Normal brain stem reflexes indicates a diffuse cortical lesion.
2. Unilateral loss of some or all reflexes indicates a focal brain stem lesion.
3. Bilateral loss of all reflexes with apnea indicates a brain death.

RESPIRATORY PATTERN

1. Normal breathing indicates a diffuse cortical lesion.
2. Cheyne-Stokes breathing is a periodic breathing with apneic spells.
3. Central neurogenic hyperventilation is characterized by deep inspiration and expiration.
4. Apneustic breathing is associated with respiratory pause after inspiration.
5. Ataxic breathing is a very irregular breathing in rate and rhythm. It is an ominous sign because the next step is apnea and brain death.

Diffuse lesions characterized by symmetric response are caused by CNS infections (meningitis or encephalitis) and encephalopathy (hypoxic, endogenous or exogenous). CT scan of the head is not essential.

Focal lesions characterized by asymmetric response are caused by intracranial hemorrhage, mass lesion (abscess or tumor) or focal ischemia and infarction. CT scan of the head is essential for diagnosis and differentiation between these lesions (see Basic Pediatric radiology). Magnetic resonance imaging (MRI) if available is more sensitive.

3. What are the associated neurological signs?

In every case of altered consciousness, other 4 neurological findings should be considered and excluded.

1. Convulsions: History, examination and follow-up for presence of convulsions are important. When present, the severity, distribution (focal or generalized), duration, frequency and response to therapy should be recorded.

2. Increased intracranial pressure: Acute rise of intracranial pressure is almost present in all comatose patients due to brain edema (cytotoxic or neurogenic) or excess volume (hemorrhage or mass lesion). The rise in pressure may be mild and undetected clinically or may be severe with serious or even fatal complications.

Clinical manifestations of acute increased intracranial pressure

Bulging anterior fontanel
It is a useful sign in neonates and infants.

Cushing response (hypertension and bradycardia)
Not constantly present.

Neurological manifestations
Sluggish pupillary reaction to light.
Increased muscle tone (hypertonia).
Exaggerated deep tendon reflexes (hyper-reflexia).
Hyperventilation with deep inspiration and expiration.

Complications or manifestations of marked Increase
Cerebral ischemia: Deterioration of the level of consciousness.
Tonic convulsions: Frequently recurrent or resistant to therapy.
Herniation syndromes.
- Central transtentorial heniation: Steady rostral-to-caudal deterioration.
- Uncal herniation: Unilatera dilated irreactive pupil.
- Cerebellar tonsils herniation through forarmen magnum: Neck rigidity.

- **Rostral-to-caudal deterioration** is detected clinically by the change of motor response from flexion withdrawal to decorticate or decerebrate extensio (see above)
- Normal intracranial pressure is 0-15 mmHg. Levels above 30 are serious.
- Intracranial pressure can be measured and continuously monitored by using intraventricular catheter, subarachnoid bolt or epidural device.
- CT scan of he head can demonstrate mass lesions, brain edema with loss of CSF spaces.

3. Lateralizing signs: Detection of structural focal lesions, which manifest by lateralizing signs, is important because urgent CT scan and neurosurgical consultation can be life saving. Motor response and cranial nerve reflexes should be made in both sides of the body. Asymmetric response should be confirmed by repeated evaluation in addition to examination of muscle tone and tendon reflexes.

Lateralizing signs in comatose patient

Focal convulsions.
Asymmetric motor response (cortical or brainstem).
Asymmetric brainstem reflexes.
Uncal herniation (unilateral dilated irreactive pupil): It is an emergency requiring urgent mechanical hyperventilation.

4. Features of meningeal irritation: They include neck rigidity, neck retraction, positive Kernig's sign and Brudziniski signs. Neck rigidity may indicate meningitis, subarachnoid hemorrhage or herniation of cerebellar tonsils through foramen magnum.

4. What are the associated physical signs?

Complete head-to-toe examination is essential as several useful findings can be detected. In comatose patient, although the coma is the most striking clinical feature several other clinical findings can be more serious and should be urgently detected and managed even before completing the examination.

Serious physical findings in comatose patient

Physical finding	Urgent management
Airway obstruction	Clear the mouth, extent the head and put an oral airway
Cyanosis, respiratory distress	Give oxygen 100%
Hypoventilation	Assisted ventilation
Shock (hypotension)	I.V line, Ringers lactate or saline (20 ml/kg in 10 minutes)
Severe hypertension	Antihypertensive drugs
Severe dehydration	I.V fluid therapy
Hyperpyrexia	Measures to lower the body temperature
Severe anemia	Urgent blood transfusion
Head trauma	Urgent CT and neurological consultation
Chest or abdominal trauma	Urgent x-ray and surgical consultation

Several other physical findings may be present. *Purpuric eruption and bleeding* may indicate intracranial hemorrhage. *Jaundice and hepatomegaly* indicate acute hepatic failure. However, in Reye syndrome (acute toxic encephalopathy with fatty infiltration of the liver), jaundice is usually absent. So, the possibility of Reye syndrome should be considered in every case of coma with hepatomegaly. *Renal mass or generalized edema* may indicate acute renal failure.

It is important to remember that **eye examination** is the most important single step in examination of the comatose patient, as several useful information can be obtained. ***The eye is the window of the brain.***

Value of eye examination in comatose patient

Evidence of the cause

Sunken eyes (dehydration), jaundice (hepatic failure), subconjunctival hemorrhage (ICH).

Pupillary changes: Pinpoint (organic phosphorus, opiates).
Small (sedatives, antihistamines, anticonvulsants).
Dilated (atropine, local instillation of mydriatics).

Level of brain dysfunction

Small reactive pupils (cortical or thalamic)
Midposition, fixed pupils (midbrain)
Pinpoint pupils (pons)

(Intact brainstem reflexes indicates that the coma is due to diffuse cortical lesion)

Evidence of lateralization

Asymmetric brainstem reflexes.
Uncal herniation (unilateral dilated irreactive pupil).

Diagnosis of brain death

Bilateral absent brain stem reflexes
- Bilateral dilated irreactive pupils (2, 3)
- Absent oculocephalic and oculovestibular reflexes (3, 4, 6, 8)
- Absent corneal reflex (5, 7)
- Absent cough/gag reflexes (9, 10)

Unresponsiveness and apnea

(Diagnosis of brain death is made if these signs persist for 12 -24 hours in absence of hypothermia, hypotension or CNS depressant drugs)

- **Oculocephalic reflex:** It is a specific reflex for comatose patients, which can test both midbrain and pontine functions. Turning the head to one side (with open eyes) results in conjugate deviation of the eyes to the opposite direction (Doll's eyes). The reflex can be elicited in the 4 directions (right, left, up and down).
  * Present reflex indicates an intact brainstem and indicates that the coma is due to a diffuse cortical disease and the brainstem is released from the cortical inhibition.
  * Absent reflex in one direction indicates a focal brainstem lesion.
  * Absent reflex in all directions indicates a brainstem death (brain death)
- **Oculovestibular reflex:** It has the same significance of oculocephalic reflex.
  * Irrigation of one auditory canal with ice water (up to 120 ml over 2 minutes) results in a conjugate deviation of the eyes towards the irrigated side. Testing of the other side should not be made except after 5 minutes.
  * Simultaneous irrigation of both ears with cold water results in downward deviation.
  * Simultaneous irrigation of both ears with hot water results in upward deviation.

  As the test is more resistant to injury it should be done if oculocephalic reflex is absent to confirm the diagnosis of brain death.

5. What is the cause?

Accurate identification of the cause of coma depends on a collection of data gained by history, examination and investigations. **History taking** should include history of head trauma, drug intoxication or insecticide, onset and course of illness. Past history of diabetes, renal disease or blood disease is particularly important. Fever with the onset of illness greatly suggests CNS infection.

Possible investigations in comatose patient

Urgent investigations (In all cases)

Blood gas analysis: In ALL cases to detect hypoxemia, CO_2 retention or metabolic acidosis.
Serum electrolytes (Na, K, Ca and Mg): To detect low or high levels.
Renal function (blood urea and creatinine): To detect acute renal failure.
Blood sugar level: To detect hypoglycemia or hyperglycemia.

Other investigations (With clinical suspicion)

Sepsis screen (CBC, ESR, CRP, blood culture): In suspected septicemia or meningitis.
Blood film for malaria: In suspected cerebral malaria.
Lumbar puncture and CSF examination: In suspected intracranial infection.
Liver function (bilirubin, transaminases, ammonia): In suspected acute hepatic failure.
Coagulation study (platelets, PT, PTT): In suspected bleeding disorder.
CT scan of the head: In head trauma or lateralizing signs.
Chest x-ray: In respiratory distress or chest trauma.
Abdominal x-ray and ultrasound: In abdominal trauma or abdominal mass.
Metabolic screen: In suspected errors of metabolism.
Toxic screen and analysis of gastric contents: In suspected poisoning.

According to presence or absence of lateralizing or focal signs, causes of coma can be generally classified into 2 groups; structural (focal) and metabolic (diffuse).

Causes of coma according to presence or absence of lateralizing signs

Structural or focal lesion	Metabolic or diffuse lesion
Intracranial hemorrhage	Meningitis and encephalitis
Focal ischemia and infarction	Encephalopathy (Hypoxic, Endogenous, Exogenous)
Mass lesion (abscess, tumor)	

Silent or isolated coma (i.e. not associated with any other neurological or physical findings) should always suggest ***exogenous encephalopathy*** (drug intoxication) as a first possibility. The possibility becomes greater when the coma is associated with small pupils and hypoventilation (slow shallow respiration with CO2 retention). It should be remembered that negative history is not conclusive as parents may deny the exposure to drugs or poisons and it should be also remembered that poisoning may occasionally be criminal (non-accidental poisoning).

Common poisons in comatose patient

Poison	Clinical manifestations
Narcotics (anticonvulsants, antihistamines)	Miosis, hypoventilation
Salicylates	Acidosis, hyperventilation
Organic phosphorus	Pinpoint pupils, increased secretions
Alcohol should be considered in adolescents	

2. Convulsions

Acute convulsions	Recurrent convulsions (Epilepsy)
Febrile convulsions	**Idiopathic epilepsy (80%)**
Simple	No evident cause
Complex (non-simple)	
CNS infections	**Organic epilepsy (20%)**
Meningitis	**Nongenetic causes**
Encephalitis	Cerebral malformations
With other diseases	Perinatal brain insult
With gastroenteritis	Neonatal or infantile brain insult
With glomerulonephritis	**Genetic causes**
With coma	Errors of metabolism
First epileptic fit	Neurocutaneous syndromes
	Degenerative brain diseases

Convulsions are among the most common pediatric emergencies and probably the most traumatic event to parents. They are defined as "involuntary contractions of muscles due to abnormal electric activity in cerebral neurons".

- What are the characters of convulsions?
- Is it acute (nonrecurrent) or recurrent (epilepsy)?
- What is the cause?

1. What are the characters of convulsions?

Description of convulsions should include the following aspects:

1. Type of convulsions: In infants and children convulsions can be:

a) Tonic: It is a rigid posturing of extremities and trunk.

b) Clonic: It is a rhythmic twitching of muscles of the face and extremities.

c) Tonic-clonic: It starts as tonic then becomes clonic. It is the commonest type.

d) Myoclonic: It is a brief jerking (sudden flexion movement) of the body and extremities. The commonest example is the infantile spasms.

2. Distribution of convulsions: Convulsions can be focal or generalized.

a) Focal convulsions: It is only involving one extremity or one side of the body and usually *not* associated with loss of consciousness.

b) Generalized convulsions: It is involving both sides of the body and it is always associated with loss of consciousness. An exception is the brief myoclonic jerks.

3. Duration and frequency of convulsions: Convulsive Fits can be *short, prolonged, status epilepticus or refractory status epilepticus* (see below). Fits can be also *infrequent* (just few fits), *frequent* (recurring several times per day) or *very frequent* (recurring every hour or less).

Clinical grading of convulsions

Grade I (Short convulsive fit): Convulsive fit lasting for few minutes (or up to 15 minutes).
Grade II (Prolonged convulsive fit): Convulsive fit lasting for 15-30 minutes.
Grade III (Status epilepticus): Convulsive fit lasting for more than 30 minutes OR Short repetitive fits without regaining of consciousness in between.
Grade IV (Refractory status epilepticus): Status epilepticus not responding to first-line anticonvulsants (Diazepm, Phenobarbital, phenytoin).

4. Effects of convulsions: During a convulsive fit, cerebral oxygen consumption increase 300% and cerebral blood flow 900%. Short and prolonged fits are not serious and are only followed by transient stupor or sleep. Status epilepticus, on the other hand, is serious and may be even fatal.

Serious effects (complications) of status epilepticus

Neurological: Cerebral ischemia, brain edema, intracranial hemorrhage.
Respiratory: Apnea, cyanosis, neurogenic pulmonary edema, aspiration (pneumonia).
Cardiovascular: Shock, heart failure, hypertension, cardiac arrest.
Metabolic: Hyperpyrexia, metabolic acidosis, hypoxemia, CO_2 retention, Hypoglycemia, hyponatremia, hyperkalemia.

Mortality rate is 5- 10% (due to apnea, cardiac arrest or brain damage).

2. Is it acute (nonrecurrent) or recurrent (epilepsy)?

Acute (nonrecurrent) convulsions are one or more convulsive fits that occur during the same acute illness and do not recur after recovery. **Recurrent convulsions (epilepsy)** are recurrent attacks of convulsions with symptom-free intervals in between. The frequency varies from one attack per year up to several attacks per day.

3. What is the cause?

A) ACUTE CONVULSIONS

In this group, febrile convulsions are the most common but other causes especially CNS infections should be excluded.

1. Febrile convulsions: It is a very common condition, which occurs in about 5% of normal children in response to rapid rise of body temperature due to extracranial infection. A genetic factor is important as positive family history of febrile convulsions can be obtained in up to 20% of cases. Diagnosis depends on 5 clinical criteria:

a) Susceptible age: It occurs between 6 months and 5 years with a peak incidence between one and half and 2 years. Convulsions below 6 months or above 5 years are not febrile convulsions.

b) Fever: Febrile convulsions occur at the onset of rapid rise of body temperature (within 8 - 12 hours of rise of body temperature). Convulsions occurring after one or two days of the onset of fever are not due to febrile convulsions. Most affected children have a temperature above 39.0°C at the time of convulsions.

c) Convulsions: The convulsive fit in *simple febrile convulsions* has the following characters: (1) Generalized tonic-clonic convulsions, (2) Brief and usually lasts for few minutes or less than 15 minutes, (3) The postictal stupor is short and frequently the patient returns to normal alertness before arrival to the hospital and (4) There is only one convulsive fit during the same illness. *Non-simple or complex febrile convulsions* occur in 10% of cases where the convulsions are unilateral, prolonged or recurring during the same illness.

d) No clinical features suggesting CNS infection: No disturbed consciousness, features of meningeal irritation or evidence of increased intracranial pressure. Clinical exclusion of these features is important.

e) Evident extracranial infection as pharyngitis, otitis media, pneumonia or gastro-enteritis. Clinical manifestations of these infections may not be clear initially but they usually appear during the next few days.

• Lumbar puncture and CSF examination is not indicated in simple cases. In complex or non-simple cases, CSF examination and exclusion of CNS infections is essential.

• Prognosis of simple cases is excellent. In about 30% of cases, a second attack will occur within a year following the first episode and in 15% of cases a third attack will occur. The risk of epilepsy is considered when:

- Convulsions recur more than 3 times or recur without fever. - Initial complex or non-simple febrile convulsions. - Positive family history of epilepsy. - Previous neurological abnormality.	EEG is indicated.

• Febrile convulsions should not be confused with other causes of fever and convulsions.

Causes of fever and convulsions

Febrile convulsions (simple and non-simple)
Toxic convulsions in gastroenteritis due to shigella, salmonella or campylobacter.
CNS infections.
Fever precipitating a convulsive fit in an epileptic child.

2. CNS infections: In meningitis and encephalitis, fever and convulsions are a common presentation. Differentiation from febrile convulsions depends on:

(a) The convulsive fits in CNS infections commonly *lack the characteristic features of febrile convulsions*, i.e. may be focal, prolonged and usually several fits occur during the

course of illness. Acute convulsions below the age of 6 months or above 5 years are mostly due to CNS infections.

(b) *Other neurological features* suggesting acute CNS lesion as disturbed consciousness, meningeal irritation or increased intracranial pressure are commonly present.

(c) *CSF examination* is essential for diagnosis.

3. Acute convulsions with other diseases: In gastroenteritis, convulsions commonly occur due to several causes but not due to CNS infection. In poststreptococcal glomerulonephritis, hypertensive encephalopathy and convulsions may be the initial presentation in some cases; so, blood pressure should be measured in every child above the age of 3 years presenting with convulsions. In comatose patient, convulsions are commonly present due to several reasons including brain edema.

Causes of convulsions in gastroenteritis

Febrile convulsions: When the onset is associated with high fever.
Toxic Convulsions: With salmonella, shigella or campylobacter infection.
Metabolic convulsions: With hypernatremic or hyponatremic dehydration.
Intracranial hemorrhage: When complicated with DIC.

4. First epileptic fit: In 5% of epileptic children, prolonged initial fit or status epilepticus is the initial presentation and in 25% of such children, fever is the sole precipitating factor. So, the possibility of epilepsy should be considered when the initial convulsive fit is prolonged or when status epilepticus is the initial presentation. EEG is indicated.

B) RECURRENT CONVULSIONS (EPILEPSY)

Children with history of recurrent convulsions or seizures are in need of detailed history, complete examination and some investigations. Evaluation of these children has 3 objectives:

1. Exclusion of epilepsy simulating conditions.
2. Diagnosis of the type of epilepsy.
3. Diagnosis of the cause of epilepsy.

1. Exclusion of epilepsy simulating conditions

Approximately, 25% of children referred to epilepsy clinics do not have epilepsy. There are many paroxysmal disorders that superficially resemble epilepsy because of associated loss of consciousness, cyanosis and/or tonic and clonic movements. Recognition of these conditions is important because treatment is different. In all these conditions, electroencephalography (EEG) is normal.

1. Breath-holding attacks: These transient attacks of apnea and loss of consciousness are mainly seen in children between 2-4 years. There are two types cyanotic and pallid. ***Cyanotic attacks*** are the common type and the attack is usually precipitated by upsetting the child. The attack starts by brief crying followed by forced

expiration, apnea, cyanosis and loss of consciousness. Within a minute, breathing returns, cyanosis disappears and consciousness is regained. The attacks are benign and not life-threatening. Reassurance of parents is important and no treatment is required. ***Pallid attacks,*** characterized by pallor, are much less common and the attacks are usually precipitated by head trauma.

2. Syncopal attacks (Fainting): These transient attacks of hypotension, cerebral ischemia and loss of consciousness are mainly seen in children above the age of 10 years. ***Simple syncope*** of vasovagal stimulation is precipitated by pain, fear, excitement or standing still for a long period. ***Cough syncope*** in asthmatic children is characterized by a paroxysmal attack of severe cough, mostly at night, followed by loss of consciousness and clonic muscular contractions for several seconds.

3. Paroxysmal vertigo: This benign condition is mainly seen in young children between 1-3 years. Typical attacks are of sudden onset, during which the child is staggering about then he falls down. Horizontal nystagmus, nausea and vomiting are commonly associated. The attack usually lasts for less than one minute. It is important to remember that consciousness is not impaired during these attacks. The condition is benign and it will subside spontaneously but these children are more susceptible to motion sickness and migraine.

4. Paroxysmal involuntary movements: ***Tics*** are paroxysmal attacks of rapid rhythmic movements usually involving the face, neck and shoulders. It is a benign transient condition. ***Benign paroxysmal torticollis of infancy*** is mainly seen in late infancy and early childhood. ***Familial paroxysmal choreoathetosis*** is rare. In all these conditions, consciousness is not impaired.

5. Paroxysmal sleep disorders: Sleep disorders as nightmares, night terrors and narcolepsy should be considered and differentiated from nocturnal seizures.

a) Nightmares are a very common condition in children. Attacks are sudden and usually occur during the *last third of night* (stage of slow wave sleep). The child screams and appears frightened but *autonomic manifestations* (tachycardia, dilated pupils and hyperventilation) are usually minimal or absent. *Arousal threshold is low* (trials to arouse the child during the attack are often successful). Within minutes the child sleeps again. In the next morning, the child often *recalls the event vividly.*

b) Night terrors are a more severe common condition occurring in 1-3% of children. Attacks are sudden and usually occur during *the first third of night* (stage of rapid eye movement) usually between 12 Midnight and 2.00 AM. The child screams and appears frightened and *autonomic manifestations* (tachycardia, dilated pupils and hyperventilation) are frequent and pronounced. *Arousal threshold is high* (failure to arouse the child). Within few minutes the child sleeps again. In the next morning, there is total amnesia of the event and the child *cannot recall* what happened last night.

c) Narcolepsy is a sudden irresistible desire to sleep that mainly occurs in adolescents. The essential feature is repetitive episodes of profound sleepiness that may occur both at rest and during periods of activity. Attacks can be long simulating epilepsy or very short (microsleeps) and misdiagnosed as attention deficit hyperactivity disorder (ADHD).

6. Pseudoseizure is a simulation of epileptic seizure by the patient. It is characterized by a more gradual onset and a bizarre movements and posture. During these false episodes there is no cyanosis, no pupillary changes and no injury to the patient as tongue biting. The condition is common in neurotic adolescent females.

2. Diagnosis of the type of epilepsy

Epilepsy is present in up to 0.5% of children. As physicians rarely witness the epileptic fit, diagnosis of epilepsy is largely dependent on accurate history. ***Full description of the epileptic fit*** should include the type, duration, frequency and effects. The history also should include the ***associated findings*** especially loss of consciousness, cyanosis, eye deviation and self-injury as tongue biting. In patients on antiepileptic drugs, the number of drugs, dosage and ***response to therapy*** should be recorded.

Practical clinical classification of the epileptic seizures is put by the international league against epilepsy in 1981 and it can be used to classify patients. Clinical diagnosis should always be confirmed by electroencephalography (EEG) to demonstrate the abnormal electrical activity.

International classification of epileptic seizures

Partial seizures	Generalized seizures
Simple partial (consciousness retained)	**Absence (Petit mal)**
Motor	Typical
Sensory	Atypical
Autonomic	
Psychic	**Tonic-clonic (Grand mal)**
	Tonic
Complex partial (consciousness impaired)	Clonic
Consciousness impaired at onset	Tonic-clonic
Consciousness impaired following simple fit	**Myoclonic**
Partial seizure with secondary generalization	**Infantile spasms**
Simple or complex	**Atonic seizures**

Unclassified seizures are seizures that cannot be easily classified.

1. Partial seizures: They occur in 40% of cases and are characterized by a focal onset (clinical and EEG). In ***simple partial seizure (SPS)***, consciousness is not impaired, seizure episode is very transient (10 - 20 seconds) and automatisms do not occur. Motor activity in the form of tonic or clonic movements is the most common symptom. In ***complex partial seizure (CPS)***, consciousness is impaired either at the onset or following the simple fit. The period of unconsciousness is usually brief. Automatisms (semipurposeful motor activities during the period of unconsciousness) are common in this type. ***Partial seizures with secondary generalization*** are characterized by a focal onset, which then spreads to involve both sides of the body. Both simple partial and complex partial may spread to become generalized.

2. Generalized seizures: They occur in 60% of cases and are characterized by absence of focal onset.

a) Absence seizures (Petit mal epilepsy): These attacks are characterized by a sudden cessation of motor activity and unresponsiveness for less than 30 seconds. The attacks may be very frequent and recurring several times per day. The condition is uncommon under the age of 5 years.

b) Generalized tonic-clonic seizures (Grand mal epilepsy): It is the commonest type and it occurs at any age. The attacks are commonly preceded by an aura. The fit starts suddenly with loss of consciousness and tonic contractions of all body musculature, which is followed by clonic contractions for few minutes. During the attacks, cyanosis, eye rolling and tongue biting may occur. The duration and frequency of the attacks vary from transient infrequent to prolonged frequent fits. Status epilepticus occur in up to 10% of cases.

c) Myoclonic epilepsy: It is characterized by sudden symmetric muscular contractions of body and extremities with loss of body tone and falling or slumping forward. There are at least 3 types with variable onset and prognosis.
(i) Benign myoclonus of infancy: It has a good prognosis.
(ii) Myoclonus of early children: Significant number has sequelae.
(iii) Complex myoclonic epilepsy: It has a poor prognosis. Delayed motor development and generalized tonic-clonic seizures in infancy usually precede the onset of myoclonus.

d) Infantile spasms (West's syndrome): It is an uncommon type, which mainly occurs during the first year. The spasm is characterized by a myoclonic jerk of body and extremities followed by tonic contractions of muscles for a few seconds. Spasms may be *flexor* (common), *extensor* (rare) or *mixed* (most common). Spasms have some characteristic features: (1) they mainly occur when the infant is drowsy or immediately upon awakening. (2) they tend to occur in clusters, i.e., the infant may have a group of 10 - 40 spasms separated from each other by a few seconds or minutes then no further episodes for the rest of the day or several hours. (3) the infant's alertness, responsiveness and development deteriorate or stop at or around the time of onset of the spasms. There are 2 groups of patients; cryptogenic and symptomatic.

(i) Cryptogenic infantile spasms occur in 20% of cases and it has a good prognosis. It is characterized by a normal history, normal neurological examination and normal CT. Remission occurs before 3 years with normal motor and mental development.

(ii) Symptomatic infantile spasms occur in 80% of cases and it has a poor prognosis (mental retardation in 80% of cases). It is characterized by an abnormal history (prenatal, natal or postnatal), abnormal neurological examination and/or abnormal CT scan of the head (see below).

e) Atonic seizures: It is characterized by sudden loss of consciousness and postural tone, which leads to sudden falls. Brief fits can be confused with myoclonic epilepsy as transient sudden falls occur in both conditions.

3. Diagnosis of the cause of epilepsy

Accurate detailed history, complete physical and neurological examination and some investigations are necessary in all cases. According to such evaluation, epilepsy can be classified into 2 groups:

1. Idiopathic epilepsy: In up to 80% of cases of epilepsy, history, examination and investigations are normal and no organic cause could be detected. It should be emphasized that the diagnosis of idiopathic epilepsy should be only made after careful exclusion of organic causes especially treatable conditions as hypoglycemia, hypocalcemia and hypomagnesemia (very important).

2. Organic or symptomatic epilepsy: In about 20% of cases, an organic cause can be detected especially when the onset of epilepsy is in infancy. It is important to remember that 80% of cases of infantile spasms belong to this group.

History, examination and investigations in organic epilepsy

History
Perinatal history (prenatal, natal and postnatal).
Neonatal and infantile brain insult: Hypoxia, hemorrhage, meningitis, trauma.
Family history of previously affected siblings.

Examination
Neurological: Especially for mental retardation and motor weakness.
Growth: Failure to thrive suggests errors of metabolism.
Skin examination: For cutaneous lesions suggesting a neurocutaneous syndrome
* Tuberous sclerosis: Hypopigmented lesions, adenoma sebaceum, Shagreen patches.
* Neurofibromatosis: Multiple cafe-au-lait spots.
* Sturge Weber disease: Unilateral facial nevus of the upper face and eyelid.

Investigations
Blood sugar, calcium and magnesium: In ALL cases.
Metabolic screen: With suspected errors of metabolism.
CT scan of the head: Especially in infants with mental retardation or motor weakness.
It is useful for detection of:
- Cerebral malformations
- Brain atrophy
- Neurocutaneous syndromes
- Degenerative brain diseases

(See CT Scan in Pediatrics)

It is important to emphasize that metabolic causes of epilepsy should be excluded in every case and diagnosis of idiopathic epilepsy cannot be made except after exclusion of these causes. ***Blood sugar, calcium and magnesium*** should be routinely done.

3. CNS Infections

Meningitis	Encephalitis
Bacterial (septic) meningitis	**Viral encephalitis**
Hemophilus Influenza type b	Enteroviruses
Meningococci, pneumococci	Mumps, herpes simplex
Other organisms	With exanthems
Viral (aseptic) meningitis	**Nonviral encephalitis**
Enteroviruses	Mycoplasma pneumonia
Mumps, herpes simplex	Protozoal
With exanthems	Fungal
Tuberculous Meningitis	**Parainfectious (allergic) encephalitis**
	Following infections
Other infections	Following vaccinations
	Unknown causes (70% of cases)

Other CNS infections include brain abscess, cerebral epidural abscess and Cerebral thrombophlebitis. Viral cerebellaritis is discussed with ataxia

Infections of the CNS are a common serious problem in pediatric practice. They are among the main causes of infant and childhood mortality and they are frequently followed by handicapping neurological sequelae.

- How to diagnose CNS infections?
- What is the type?
- How to confirm the clinical diagnosis?
- What are the complications and sequelae?

1. How to diagnose CNS infections?

Clinical manifestations of CNS infections can be classified into 2 groups; general manifestations of acute infection and specific manifestations of acute CNS disease.

1. Evidence of acute infection: Fever, anorexia, vomiting, constipation and irritability are usually present. High fever, toxemia and purpuric skin rash should always suggest the diagnosis of "meningococcemia".

2. Evidence of acute CNS disease: Infections of the CNS may present clinically with one or more of the following 5 neurological findings. Presence of any one should stimulate the search for the other 4.

a) Altered consciousness: Various degrees of disturbed consciousness may occur ranging from lethargy to deep coma. Occasionally, abnormal bizarre behavior (disturbed memory, phobias, aggressive behavior, hallucinations etc.) are the only neurological manifestations in some cases of encephalitis.

b) Convulsions: Focal or generalized tonic-clonic convulsions may occur with variable severity and frequency. Usually more than one fit occur during the course of illness, which is an important differentiating point from febrile convulsions.

c) Increased intracranial pressure: *Severe persistent vomiting* and/or *severe headache* especially when associated with other neurological findings should always suggest an increased intracranial pressure. In infants, bulging fontanel is the most important sign while in children *bradycardia and hypertension* are suggestive. Suspicion is confirmed by fundus examination (papilloedema) and cautious lumbar puncture (increased pressure). In comatose patient, several other manifestations and complications of increased intracranial pressure may occur (see comatose child).

d) Features of meningeal irritation: These features are present in meningitis. They may be mild (as in aseptic meningitis) or well evident (as in septic and tuberculous meningitis).

Features of meningeal irritation

Neck rigidity, ± neck retraction.
Brudzinski neck sign: If the neck is flexed, the hips will be also flexed.
Brudzinski leg sign: If one hip is flexed, the other hip will be flexed.
Kernigs sign: If hips are flexed, the knees can not be extended.
Arching of the back (opisthotonos) occurs in severe cases.

e) Lateralizing signs: Focal paralysis or unequal pupils may occur in some cases due to focal ischemia and infarction or in case of brain abscess. Facial and ocular paralysis may be also present especially in tuberculous meningitis.

2. *What is the type (meningitis, encephalitis or brain abscess)?*

Clinical differentiation between different types depends on the following:

- Onset of illness and degree of fever.
- Main neurological signs
- Other characteristic features
- Course of illness.

1. Bacterial (septic or purulent) meningitis: It is characterized by:

- The onset is usually abrupt with high fever and vomiting. The patient appears critically sick with marked toxemia.
- Convulsions and meningeal irritation are the main neurological signs. In infants convulsions are common while features of meningeal irritation are less evident. In children, features of meningeal irritation are more frequent than convulsions.

• In meningococcal meningitis, high fever, toxemia and purpuric skin rash may be the main presentation (meningococcemia).

• The course may be fulminant and unless urgent proper management is initiated, death or serious neurological sequelae may occur.

2. Viral (aseptic) meningitis: It is characterized by:

• The onset is acute with mild to moderate fever and may be vomiting but the patient does not look critically sick as those with bacterial meningitis.

• Mild meningeal irritation (neck rigidity) is the only neurological finding. Convulsions are rare in absence of an encephalitic element (don't make the diagnosis of aseptic meningitis in presence of convulsions).

• Preceding or concomitant exanthem (as herpes simplex or chickenpox) may be present. Mumps also is an important common cause.

• The course is benign and complete recovery is the rule.

3. Encephalitis or meningoencephalitis: It is characterized by:

• The onset is usually acute with fever and may be vomiting.

• Abnormal bizarre behavior and/or altered consciousness are the most evident neurological findings. In some cases presenting with fever and coma (as the only neurological finding) the clinical diagnosis of encephalitis can be made. In case of meningoencephalitis, convulsions and increased intracranial pressure are common and clinical differentiation from bacterial meningitis cannot be made.

• Preceding or concomitant exanthem may be also present. In mycoplasma encephalitis, a preceding lobar pneumonia is usually present. In allergic encephalitis, history of an exanthem or vaccination few weeks before the onset of illness can be obtained.

• The course is extremely variable and it is ranging from rapid complete recovery within a few days to a prolonged coma, severe neurological sequelae or death.

4. Tuberculous meningitis: It is characterized by:

• The onset is insidious and is characterized by a nonspecific features as mild fever, irritability, vomiting and constipation which remain for about one week before the appearance of neurological manifestations. So, tuberculous meningitis is usually not confused clinically with bacterial meningitis or viral meningoencephalitis.

• The illness can be divided into 3 stages, each for 1 - 2 weeks:

- ***Stage I (prodromal stage):*** Nonspecific manifestations of infection.

- ***Stage II (transitional stage):*** Convulsions, meningeal irritation and cranial nerve palsies as ocular and facial paralysis.

- ***Stage III (terminal stage):*** Hyperpyrexia and deep coma. Death usually occurs if the patient reaches this stage (tuberculous meningitis is the only fatal form of tuberculosis).

• Other manifestations suggesting tuberculosis as weight loss, lymphadenopathy and/or chronic chest disease may be evident.

• With early diagnosis (during the first or early second stage) and proper treatment, recovery is possible with minimal sequelae.

5. Brain abscess: This uncommon infection is characterized by the following:

- The onset is usually insidious over several days with fever and vomiting.
- Increased intracranial pressure (headache, vomiting) and lateralizing signs (focal paralysis) are the main neurological findings.
- Preceding or concomitant bacterial infection as septicemia, empyema or otitis media may be present. Polycythemia as in congenital cyanotic heart diseases is sometimes the main predisposing factor.
- The course is usually prolonged over weeks. If it ruptures, fatal meningitis may occur.
- With clinical suspicion, CT scan of the head is important for diagnosis (hypodense lesion with ring enhancement) and localization (See CT scan in Pediatrics).

3. *How to confirm the clinical diagnosis?*

1. CSF examination: Cautious lumbar puncture is made with a narrow needle and while the patient is lying on his side to avoid medullary herniation. Examination of the cerebrospinal fluid (CSF) should include the pressure, cells, proteins, sugar and culture for bacteria (see below). A second examination should be made after 24-48 hours to evaluate the response to therapy and a third one is made at the end of therapy.

2. Other investigations: *Complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)* are useful in differentiation between bacterial meningitis and viral encephalitis. In bacterial meningitis, polymorphonuclear leukocytosis, high sedimentation rate and elevated C-reactive protein are commonly present. Tuberculin test and chest x-ray are indicated in suspected tuberculous meningitis. *CT scan of the head* is indicated in suspected brain abscess or in presence of lateralizing signs.

4. *What are the complications and sequelae?*

1. Death: Fulminant bacterial meningitis, encephalitis, untreated tuberculous meningitis and ruptured brain abscess may lead to death.

2. Blindness and deafness: They are common sequelae of fulminant bacterial meningitis. Evaluation of vision and hearing is important.

3. Neurological sequelae: One or more of 5 sequelae may occur:

1. Mental retardation (due to cerebral damage).
2. Organic epilepsy (due to development of epileptogenic focus).
3. Motor weakness (due to cerebral damage).
4. Hydrocephalus (due to subdural adhesions).
5. Bilateral subdural effusion (with bacterial meningitis).

In every case of CNS infection, and after recovery, ***periodic neurological assessment*** of mental development, motor development and head size are essential. Progressive increase in head size (in infants) or manifestations of increased intracranial pressure should suggest postmeningitic hydrocephalus or subdural effusion. CT scan of the head is indicated for early detection of these complications.

CSF findings in CNS infections

	Pressure (40-80 mm H_2O)	Leukocytes ($2\text{-}4/mm^3$)	Protein (20 -40 mg/dl)	Glucose (40-80 mg/dl)
Bacterial meningitis	Increased	100- 50000 (PMN)	100 –500	↓ (< than 40)
Viral meningitis	Normal or ↑	Less than 1000 (mononuclear)	50 – 200	Normal or ↑
Viral encephalitis	Normal or ↑	Less than 1000 (PMN early, then mononuclear)	50-200	Normal or ↑
T.B meningitis	Increased	10- 500 (lymphocytes)	100 - 500	↓ (< than 40)
Brain abscess	Increased	10-200 (lymphocytes)	100-500	Normal

Remarks

1. Turbid CSF with leukocyte count above 1000 usually indicates bacterial meningitis. In partially treated bacterial meningitis, CSF findings may resemble those of aseptic meningitis where the mononuclear cells predominate.
2. CSF with cell count between 500-1000 (and mainly polymorphonuclear) is either due to bacterial meningitis or viral encephalitis. Glucose level is important for differentiation in addition to CBC, ESR and CRP.
3. In tuberculous meningitis and brain abscess, cells are mainly lymphocytes. Glucose level is depressed in tuberculous meningitis.
4. Protein content is not useful in suggesting any pathology.
5. Completely normal CSF does not exclude viral encephalitis.
6. Simultaneous determination of blood glucose is important for proper evaluation of CSF glucose. Normally, CSF glucose is 75% the blood glucose. CSF glucose level is decreased in bacterial and tuberculous meningitis.
7. Microscopic examination of CSF for bacteria or parasites (malaria or amoebiasis) is important. CSF cultures for bacteria is essential. Cultures for viruses and fungi, if available, may be useful.

4. Acute Paralysis

Acute asymmetric	Acute symmetric	Acute hemiplegia
Poliomyelitis	Guillain-Barre syndrome	Infections
Nonpolioenteroviruses	Postdiphtheritic paralysis	Extracranial
Postinjectional paralysis	Botulisim	Intracranial
Pseudoparalysis	Transverse myelitis	Cardiac
Trauma	Spinal cord compression	Hematologic
Toxic synovitis	With ataxia or chorea	Metabolic
Osteomyelitis	Rare causes (Rabies, Tetanus, porphyria)	Traumatic
		Arteriovenous malformations

CNS infections can produce any form of paralysis but manifestations of acute brain insult are the dominating signs

Acute severe motor weakness in a previously normal infant or child is a common clinical presentation in pediatric practice. Loss of motor functions usually occurs over few hours or few days.

- What is the extension of paralysis?
- What are the associated manifestations?
- What is the cause?

1. *What is the extension of paralysis?*

Acute paralysis can involve one or more of the following sites:

1. Peripheral paralysis: It is the commonest form. According to the distribution, acute paralysis can be *asymmetric, symmetric or hemiplegic* (Accurate examination of the 4 limbs is important). The affected limb or limbs show hypotonia, hyporeflexia and loss of movements. In acute spinal cord lesions, gradual change to hypertonia and hyperreflexia occurs over several weeks.

2. Respiratory paralysis: Paralysis of respiratory muscles (diaphragm and intercostal muscles) is a serious life-threatening form, which may occur in some cases of poliomyelitis, Guillain-Barre syndrome, postdiphtheritic paralysis and botulism. Clinical manifestations include anxious expression, shallow rapid breathing and inability to speak without frequent pauses. ***Diaphragmatic paralysis*** is characterized by the paradoxical breathing where the abdomen collapses during inspiration and distends during expiration (seesaw abdominal movements). Diaphragmatic function can be clinically assessed by manual splinting of the thoracic cage and observing the abdominal movements. Clinical diagnosis can be confirmed by blood gas analysis to demonstrate the hypoventilation and CO_2 retention ($PaCO_2$ above 60 mm Hg).

3. Bulbar paralysis: It is a potentially serious form, which may occur in some cases of poliomyelitis, Guillain-Barre syndrome, postdiphtheritic paralysis, botulism and rabies. Clinical manifestations include (1) weak nasal cry, (2) weak ineffective cough, (3) nasal regurgitation of saliva and fluids due to palatal paralysis, (4) accumulated pharyngeal secretions with inability to clear the pharynx due to poor swallowing and weak cough. This can lead to aspiration and airway obstruction, (5) paralysis of vocal cords can lead to aphonia or stridor. (6) Paralysis of vital brainstem centers can lead to irregular respiration, fluctuations in blood pressure and rapid change in body temperature, (7) in unilateral lesions, deviation of palate, uvula and tongue can occur.

The sequence of paralysis is also important:

a) Ascending paralysis (lower limbs, trunk, upper limbs then respiratory and bulbar) is characteristic of Guillain Barre syndrome and poliomyelitis.

b) Descending paralysis (bulbar, respiratory then peripheral) is characteristic of post-diphtheritic paralysis, botulism. Occasionally, Guillain barre syndrome can be atypical and produces descending paralysis.

2. *What are the associated manifestations?*

History of trauma, fever, preceding infections and vaccination is important.

Other neurological findings especially *sensory loss* and *autonomic dysfunction* should not be overlooked. These findings are particularly common is spinal cord lesions as transverse myelitis and spinal cord compression. *Disturbed consciousness* and *hemiconvulsions* are common initial associated findings in acute hemiplegia.

Examination of limbs should include a search for fracture, focal tenderness, focal swelling and painful limping gait. This is particularly important in case of monoplegia as pseudoparalysis is a common cause of confusion.

3. *What is the cause?*

Although diagnosis of the cause can be made on clinical basis, some investigations are sometimes needed for precise diagnosis and for differentiation between conditions presenting with similar findings.

Possible investigations in acute paralysis

CSF examination: In suspected CNS infection or Guillain Barre syndrome.
Nerve conduction velocity: In tetraplegia to diagnose peripheral neuritis.
Electromyography: In polyneuritis and in suspected botulism (characteristic).
Myelography: In paraplegia to differentiate between transverse myelitis and spinal cord compression. CT scan or MRI are also very useful.
CT scan of the head or MRI: In every case of acute hemiplegia.
Four vessel cerebral angiography: In vascular hemiplegia.

A) ACUTE ASYMMETRIC PARALYSIS

In this group, paralysis is either limited to one limb (nonoplegia) or involving both sides with asymmetric distribution.

1. Poliomyelitis: It is a viral disease of the anterior horn cells. In underdeveloped countries, it was a common cause of acute paralysis especially in unvaccinated or partially vaccinated infants and young children. Recently, the disease becomes very rare or nearly eradicated.

- ***Characters of paralysis:*** In poliomyelitis, paralysis is *sudden* (occurs within few hours), *massive* (involves lower limbs, trunk and other areas), *flaccid* (severe hypotonia), *asymmetric* (more on one side) and *purely motor* (no sensory loss).
- ***Extension of paralysis:*** *Spinal poliomyelitis* is the commonest form. Asymmetric paralysis of the lower limbs is the most common. Paralysis may extend to affect the trunk, upper limbs and neck. Respiratory paralysis due to intercostal and diaphragmatic paralysis may occur and can be life-threatening. In *spinobulbar poliomyelitis*, bulbar paralysis (weak cry, weak cough and nasal regurgitation) are also present.
- ***Stages of paralysis:*** In poliomyelitis, paralysis passes through 3 stages:

(i) Acute stage (first 2 weeks): During this stage, the patient is infectious (isolation is important) and paralysis may extend to involve other areas (observation is important). As intramuscular injections may precipitate more paralysis, it is important to avoid injections during this stage. This stage is the stage of *"pediatrician"*.

(ii) Restoration stage (2 weeks to 6 months): During this stage, gradual, but incomplete, recovery usually occurs. Physiotherapy, 2-3 times per week, is very important to prevent muscle wasting and deformities. This stage is the stage of *"physiotherapist"*.

(iii) Stage of residuals (after 6 months): During this stage, no further improvement is expected and residuals as wasting, shortening and deformities usually occur in severe and neglected cases. Stage of residuals is the stage of *"orthopedic surgeon"*.

2. Nonpolio enteroviruses: Occasionally, coxsackie viruses and echoviruses can affect the anterior horn cells and cause acute paralysis. However, paralysis due to these viruses is usually *mild, not massive* and *transient*. The possibility should be considered in vaccinated infants and children presenting with mild paralysis.

3. Postinjectional paralysis: In this case, paralysis is limited to the limb where the injection is given *(monoplegia)*. It may be associated with radiating pain along the course of the injured sciatic nerve. The condition can be confused with mild poliomyelitis as in poliomyelitis paralysis may be precipitated by injections. The focal nature of the lesion and the absence of paralysis in other areas usually help in differentiation.

4. Pseudoparalysis: Although it is not a true paralysis, it can be confused with mild unilateral paralysis. It may follow unrecognized trauma (fracture, sprain or contusion), toxic synovitis of the hip or the knee (see arthritis) or acute osteomyelitis. Affected children usually present with a *painful limping gait*. Careful examination may reveal a *focal tenderness*. Neurological examination is free.

B) ACUTE SYMMETRIC PARALYSIS

In this group, bilateral symmetric involvement is the rule. Paralysis is either affecting both lower limbs (paraplegia) or the 4 limbs (tetraplegia or quadriplegia). Paraplegia is mostly caused by acute spinal cord disease (transverse myelitis or cord compression) while tetraplegia is mostly due to peripheral neuritis (Guillain Barre syndrome, postdiphtheritic paralysis) or botulism. A search for movement disorder as ataxia or chorea is important because in these conditions hypotonia is occasionally severe and dominating the picture.

1. Guillain Barre syndrome (postinfectious polyneuritis): It is by far the most common cause of acute paralysis in children. Although infants can be affected, most cases are seen in children above the age of 3 years. History of preceding viral infection, one or two weeks before the onset of paralysis, is usually obtained. The important characteristic features are:

- ***Acute symmetric paralysis:*** Paralysis starts in lower limbs and usually ascends over few days to involve the trunk and upper limbs *(tetraplegia)*. Affected limbs are flaccid with lost tendon reflexes. *Respiratory paralysis* may occur in some cases and necessitates hospitalization and mechanical ventilation for weeks. *Bulbar paralysis* occurs in 50% of cases and can lead to aspiration and pneumonia. Atypical forms of paralysis with descending nature (bulbar, respiratory then peripheral) may occur.
- ***Other neurological findings:*** Peripheral sensory loss is minimal or absent and autonomic disturbance as urinary retention may occur. Occasionally, initial disturbed consciousness for hours or few days may occur.
- ***The course*** is benign in most cases and gradual complete recovery usually occurs over few weeks or few months. Relapses may occur in 10% of cases.
- ***Confirmatory investigations*** include nerve conduction velocity (markedly reduced) and CSF examination 2 weeks after onset (increased CSF proteins).

2. Postdiphtheritic paralysis: This form of toxic polyneuritis is relatively uncommon nowadays because of the routine vaccination. History of preceding sore throat and swollen neck (pharyngeal diphtheria) or stridor (laryngeal diphtheria), 1-2 weeks before the onset of paralysis can be obtained.

- Paralysis is usually descending. Ocular and bulbar paralysis is the initial presentation, which can be followed by peripheral paralysis of limbs after one or 2 weeks. Paralysis is characteristically purely motor and transient.
- The course is benign and complete recovery occurs over few weeks. The initial bulbar involvement, absence of sensory involvement can differentiate the condition from Guillain Barre syndrome.

3. Botulism: It is a toxic neuromuscular blockade caused by clostridium botulinum (anaerobic gram positive bacteria). According to the type of infection, 3 forms are present: (1) ***Infant botulism*** occurs in infants with peak incidence between 2 to 6 months. Germination of spores in gastrointestinal tract follows exposure to soil, house

and honey or corn syrup. *(2)* ***Food-borne botulism*** occurs with ingestion of improperly home-preserved foods containing the *toxins*. *(3)* ***Wound botulism*** occurs due to wound contamination with the clostridium botulinum organisms.

- Paralysis is *acute, symmetric and descending.* It starts in bulbar nerves then descends over a period of few hours or few days to involve the trunk and limbs. Respiratory paralysis is common and usually necessitates prolonged mechanical ventilation. Paralysis is purely motor with no sensory involvement.
- Affected patients are usually alert, afebrile with dry mucous membranes of mouth, tongue and pharynx. Lacrimation is also decreased.
- The course of illness is usually prolonged over several weeks. Prolonged mechanical ventilation for months is not unusual.
- CSF and nerve conduction velocity are normal (important differentiating points from atypical form of Guillain Barre syndrome with descending nature). The most important diagnostic investigation is the electromyography, which demonstrates the characteristic brief, small, abundant motor-unit action potentials (BSAP).

4. Transverse myelitis: It is the second most common cause of acute symmetric paralysis. It is a segmental dysfunction of the spinal cord without an evidence of spinal cord compression. The cause is probably either a direct viral infection or an autoimmune disease.

- Paralysis is acute, symmetric and usually involving only the lower limbs (paraplegia). In rare situations where the lesion is above the 5th cervical segment, involvement of upper limbs also occurs (quadriplegia). Initially, paralysis is flaccid but gradual change to spasticity occurs over few weeks.
- Sensory loss (with sensory level on the trunk) and autonomic disturbance (urinary retention and stool incontinence) are usually present.
- The course is usually prolonged over several months. Complete recovery occurs in only 60% of cases.
- Myelography (or MRI of the spine) is important for differentiation from acute spinal cord compression. It is normal in transverse myelitis.

5. Acute spinal cord compression: Trauma to the back, spinal epidural abscess and vascular anomalies of the cord may produce a picture, which can not be clinically differentiated from transverse myelitis. Occasionally, spinal cord tumors may also present with acute paralysis. Myelography is essential to demonstrate the obstruction. CT scan of the spine or MRI are more sensitive and can show the nature of obstruction.

6. With movement disorders: In ***acute cerebellar ataxia,*** hypotonia is usually present and may be prominent but the truncal ataxia with unsteady gait is the most characteristic feature. In ***rheumatic chorea,*** hypotonia is present and may be marked mimicking acute paralysis but abnormal involuntary choreic movements are the dominating finding.

7. Other causes: Rare causes of acute paralysis include rabies, tetanus, porphyria and familial periodic paralysis.

a) Rabies is characterized by a history of an animal bite, few weeks to few months before the onset of illness. Marked excitability, hydrophobia and aerophobia are characteristic early features. Painful spasms, convulsions and ascending paralysis usually follow. Coma and death is the final event in all cases.

b) Tetanus is characterized by trismus, painful spasms and normal consciousness. The absent hydrophobia and the present trismus differentiate it from rabies. Recovery usually occurs in many patients especially with the modern intensive care therapy.

c) Porphyria is a rare autosomal dominant disease, which is very rare before puberty. It is characterized by recurrent attacks of colicky abdominal pain, which may be associated with paralysis and painful tender muscles.

d) Familial periodic paralysis is also a rare autosomal dominant disease characterized by recurrent episodes of transient paralysis for few or several hours only. It has 2 types (the hypokalemic and the hyperkalemic types).

C) ACUTE HEMIPLEGIA

Acute hemiplegia (stroke) in children is mostly seen below the age of 6 years with a peak incidence between 1 - 3 years. However, it may occur at any age.

The main pathology is a focal lesion in one hemisphere, which results in focal ischemia and necrosis.

Types of acute hemiplegia (according to the mechanism)

Vascular hemiplegia (most common)
- Cerebral thrombosis (Venous or arterial): Due to infection or polycythemia.
- Cerebral embolism Mostly due to cardiac disease.
- Cerebral hemorrhage: Due to blood disease, ruptured aneurysm or vascular malformations.

Inflammatory hemiplegia
- Focal encephalitis.
- Brain abscess.

Traumatic hemiplegia
- Brain contusion or laceration.
- Subdural or subarachnoid hemorrhage.
- Intracerebral hemorrhage.

- **The onset** of hemiplegia varies according to the mechanism. It may be *sudden* (embolism), *acute* (thrombosis, hemorrhage) or *more gradual* over several hours or few days (infection). It is sometimes *intermittent or stuttering* with transient episodes of weakness (as in carotid artery thrombosis).

- **Clinical manifestations** of acute hemiplegia include *weakness and hyptonia* of the affected side, which is more marked in the face and upper limb. Tendon reflexes are weak or absent but Babiniski sign is frequently positive.

- **Associated neurological manifestations** depends on the level of dysfunction:

a) Cerebral lesions are commonly associated with hemiconvulsions (hemiplegia hemiconvulsion syndrome), transient loss of consciousness and transient aphasia. Capsular lesions are associated with hemianesthesia and upper motor neurone lesion of the face and tongue on the affected side.

b) Brain stem lesions are associated with ocular paralysis (midbrain and pons) or bulbar paralysis (medulla) on the other side of the lesion (LMNL).

- **Diagnostic investigations:** *CT scan of the head or MRI* is important in every case for proper localization and identification of the nature and extent of the lesion (infarction, inflammation, abscess or hemorrhage). *Cerebral angiography* is also very useful. *Echocardiography* should be also a routine investigation in every case of sudden hemiplegia as cerebral embolism or thrombosis commonly occurs on the top of cardiac lesion.

- **The cause** of hemiplegia can be identified by history, examination and appropriate investigations.

a) Infections: Extracranial infections as otitis media, orbital cellulitis, cervical adenitis and respiratory infections can produce cerebral thrombophlebitis and hemiplegia. It is the commonest cause. *Intracranial infections* as bacterial meningitis, focal encephalitis or brain abscess may also present with acute hemiplegia. CSF examination is indicated with clinical suspicion.

b) Cardiac causes: Congenital cyanotic heart diseases (cerebral thrombosis), infective endocarditis (cerebral embolism) are the main causes. Arrhythmias especially AF may also lead to cerebral embolism. Paradoxical embolism may occur from pelvic veins through intracardiac shunt.

c) Hematological causes: Intracranial hemorrhage may occur in hemophilia, DIC, idiopathic thrombocytopenic purpura or aplastic anemia.

d) Metabolic causes: Severe hypernatremic dehydration may be complicated with cerebral thrombosis and hemiplegia.

e) Traumatic causes: Head trauma can lead to brain contusion, laceration or intracranial hemorrhage. Blunt nonpenetrating trauma to the paratonsillar area (falling with a pencil or stick in the mouth) can produce internal carotid artery thrombosis and hemiplegia.

f) Spontaneous rupture of aneurysm (or arteriovenous malformations) should be considered in unexplained cases.

- **Prognosis** is generally not good. Residual paralysis, mental retardation and organic epilepsy occur in 50% of cases.

5. Floppy Infant

Central (Brain) causes	Neuromuscular causes
Atonic cerebral palsy	Werdnig-Hoffmann disease
Chromosomal diseases	Congenital muscular dystrophy
Other causes	Congenital myopathies
Lowe syndrome	Glycogenosis type II (Pompe disease)
Pradder-Willi syndrome	Neonatal myasthenia gravis
Leukodystrophies	Benign congenital hypotonia
Cerebral anomalies	

Floppy infant is an infant with severe persistent hypotonia present at birth or in early infancy. Conditions causing acute paralysis and severe hypotonia (as poliomyelitis, Guillain Barre syndrome and spinal cord trauma) are not included because the infant was normal before the onset of paralysis.

- How to diagnose floppy infant?
- Is it central or neuromuscular?
- What is the cause?

1. How to diagnose floppy infant?

Diagnosis of severe hypotonia depends on the presence of the following signs denoting hypotonia of limbs, trunk and neck.

1. Frog-leg position: In supine position, the limbs are abducted and slightly flexed simulating frog legs. This denotes hypotonia of limbs.

2. Curved trunk on ventral suspension: When the baby is suspended in prone position over the examiner's palm, he droops around it. This denotes hypotonia of the trunk muscles.

3. Head lag: When the baby is pulled up from his hands, while in supine position, the head lags backwards. This denotes hypotonia of neck muscles.



Frog-leg position | **Ventral suspension** | **Head lag**

2. *Is it central or neuromuscular?*

Clinical differentiation between central and neuromuscular causes depends on deep tendon reflexes and mental development.

Central causes are characterized by a *normal or exaggerated tendon reflexes.* Mental retardation is common and recurrent convulsions may be also present.

Neuromuscular causes are characterized by a *weak or absent tendon reflexes.* Mental development is usually normal.

3. *What is the cause?*

Although the cause can be suggested in most cases, some investigations are required for precise diagnosis and for differentiation between conditions presenting with similar findings.

Possible investigations in floppy infant

In suspected central disease
- CT scan of the head: May reveal brain atrophy, cerebellar anomalies or degenerative disease.
- Chromosomal karyotype: In suspected chromosomal disease.
- Serum copper and ceruloplasmin levels: Low in kinky hair disease.

In suspected neuromuscular disease
- Creatine phosphokinase (CPK): Elevated in muscular dystrophy.
- Nerve conduction velocity: Reduced in peripheral neuritis.
- Electromyography (EMG): Vibrillation potentials in Werdnig-Hoffmann disease.
- Muscle biopsy: To differentiate between myopathies and dystrophy.

A) CENTRAL CAUSES

In this group, clinical examination should include primitive neonatal reflexes and search for abnormal features, cataract, obesity and hair changes.

1. Atonic cerebral palsy: Cerebral palsy is a term used to describe a heterogenous group of disorders characterized by nonprogressive motor weakness resulting from a defect or lesion of the developing brain. According to the type of motor weakness, it is classified as atonic, spastic, extrapyramidal and mixed.
- The most important characteristic feature is the persistence of primitive neonatal reflexes as Moro reflex and grasp reflex (see neonatal reflexes).
- Associated neurological signs, as mental retardation, epilepsy, squint and/or pseudo-bulbar palsy are common. Microcephaly may be also present.
- Causes of cerebral palsy are the same causes of nongenetic mental retardation (i.e. prenatal, natal and postnatal). Careful perinatal history is important.
- CT scan of the head may demonstrate brain atrophy.
- It should be remembered that diagnosis of cerebral palsy is only made after careful exclusion of other central causes.

2. Chromosomal diseases: Several trisomies and deletion syndromes may be associated with marked hypotonia. The possibility should be considered in the presence of abnormal features (face, hand and foot) and low birth weight. Chromosomal karyotype is indicated with clinical suspicion.

3. Other causes: Rare central causes of floppy infant include *Lowe syndrome* (hypotonia, cataract and later development of rickets), *Pradder-Willi syndrome* (hypotonia, obesity, ± diabetes) and some *leukodystrophies* (as kinky hair disease and neonatal adrenoleukodystrophy). Kinky hair disease is characterized by hypotonia, myoclonic seizures, kinky colourless friable hair and low serum copper and cerulo-plasmin levels (see also spastic infant). *Congenital anomalies of the cerebellum* may present in infancy with severe hypotonia. CT scan is important for exclusion.

B) NEUROMUSCULAR CAUSES

In this group, clinical examination should include a search for tongue fasciculations, muscle wasting and joint contractures.

1. Werdnig-Hoffmann disease: It is the commonest cause of floppy infant. It is an autosomal recessive disease characterized by degeneration of anterior horn cells. It is characterized by the following:

- Floppy infant with absent tendon reflexes.
- Bulbar palsy: Weak cough and weak cry.
- Visible tongue fasciculations: Worm-like movements due to denervation of muscles.
- Normal mentality and eye movements.
- Late respiratory paralysis: Most cases die in the first 2 years by respiratory paralysis.
- Diagnosis can be confirmed by EMG and muscle biopsy.

2. Congenital muscular dystrophy: It is an autosomal recessive disease characterized by degeneration of muscles. It is characterized by the following:

- Floppy infant with weak or absent tendon reflexes.
- Thin muscles of the limbs and trunk.
- Joint contractures and arthrogryposis are common.
- Prognosis depends on the severity of illness. Severe forms are fatal in infancy while mild forms are benign and not progressive.
- Diagnosis is confirmed by muscle biopsy. CPK is moderately elevated but not reliable for diagnosis because it may be extremely high in normal newborns.

3. Congenital myopathies: These are a group of congenital muscle diseases with variable inheritance, severity and outcome. Some forms are benign while others are progressive and fatal in early infancy. The main characters of these diseases are:

- Floppy infant with weak or absent tendon reflexes.
- Thin muscle bulk of the limbs and trunk.
- Mild joint contractures may be present.
- Variable ocular, facial and respiratory weakness.
- Diagnosis and prognosis depends on muscle biopsy which can differentiate between different types. CPK, EMG and nerve conduction velocity are all normal.

Congenital myopathies	
Fatal diseases	**Benign diseases**
Myotubular myopathy	Central core disease
Congenital muscle fibre-type disproportion (CMFTD)	Multicore (minicore) disease
Severe forms of nemalin rod myopathy	Nemalin rod myopathy

- In fatal forms, respiratory paralysis is the cause of death.

4. Glycogenosis type II (Pompe disease): It is an autosomal recessive disease characterized by excessive accumulation of glycogen in the muscles, heart and liver. It presents clinically in the neonatal period with extreme hypotonia (floppy infant), thick protruding tongue and cardiomyopathy (cardiomegaly, cyanosis, heart failure but no murmurs). The clinical course is rapidly progressive and cardiorespiratory failure leads to death in infancy.

5. Congenital myasthenia gravis: It is a rare disease of neuromuscular junction caused by antibodies against acetylcholine. It is the only curable disease of all neuromuscular causes of floppy infant. It manifests in neonatal period with hypotonia, weak suckling, shallow respiration and ptosis (eyelids and extraocular muscles are the most severely affected). The condition should be suspected in presence of ptosis and ophthalmoplegia. A clinical therapeutic test is the administration of short-acting cholinesterase inhibitor (edrophonium, 0.2 mg/kg, I.V.). Immediate improvement of ptosis and ophthalmoplegia occurs for 1 - 2 minutes. Electromyography is characteristic and diagnostic. Treatment is by oral prostigmine or pyridostigmine. Treatment is lifelong. The condition should be differentiated from transient neonatal myasthenia of infants born to myasthenic mothers.

6. Benign congenital hypotonia: It is a term used to describe infants with nonprogressive hypotonia of unknown etiology. Such diagnosis is only made after careful clinical and laboratory exclusion of all other causes. Normal muscle biopsy and CT scan of the head are essential for diagnosis. Although hypotonia persists into adult life, it is not associated with weakness or delayed motor development. Contractures do not occur and mentality is normal.

6. Spastic Infant

Spastic cerebral palsy (monoplegic, paraplegic, hemiplegic, triplegic, quadriplegic)
Acquired brain insult (postmeningitic, postencephalitic, post-hypoxic)
Neglected hydrocephalus
Leukodystrophies (especially Krabbe disease or globoid leukodystrophy)

Spasticity in infancy is a common neurological presentation. Clinical manifestations include increased muscle tone (spasticity), exaggerated tendon reflexes (hyper-reflexia) and commonly sustained ankle clonus.

Clinical evaluation should include accurate perinatal history, history of acquired brain insult (CNS infection, hypoxia), head circumference and course of illness.

CT scan of the head is extremely useful in differentiation between different causes. It may show brain atrophy (cerebral palsy, acquired brain insult), hydrocephalic changes (hydrocephalus) or degeneration of while matter (leukodystrophies).

1. Spastic cerebral palsy: It is by far the commonest cause of spasticity in infants. It is characterized by the following:

- ***Distribution of spasticity*** is variable. It may be *monoplegic* (only one limb is affected), *paraplegic* (two limbs, usually the lower limbs), *hemiplegic* (one side is affected with more spasticity of the upper limb), *triplegic* (three limbs are affected) or *quadriplegic* (the four limbs are affected). Quadriplegia is either diplegia (spasticity is more in lower limbs) or double hemiplegia (spasticity is more in upper limbs). With severe spasticity of lower limbs, scissoring of lower limbs occurs and ankle clonus becomes evident.
- ***Degree of motor dysfunction*** is variable. It may be absent (class 1), mild (class 2), moderate (class 3) or severe (class 4). Evaluation of motor function (motor development) is important.
- ***Associated neurological signs*** as mental retardation, epilepsy, squint and/or pseudo-bulbar palsy are common. Microcephaly may be also present. Persistence of primitive neonatal reflexes is characteristic.
- ***Causes*** of cerebral palsy are the same causes of nongenetic mental retardation (i.e., prenatal, natal and postnatal). Accurate perinatal history is important.
- It should be remembered that diagnosis of cerebral palsy is only made after careful exclusion of other causes of spasticity.

2. Acquired brain insult: Severe brain insult is commonly followed by motor weakness and spasticity especially when the onset is associated with deep prolonged coma. Severe bacterial meningitis and encephalitis are common causes. Severe hypoxic encephalopathy following cardiopulmonary arrest, severe airway obstruction or severe respiratory failure is also a common cause. History of previous severe illness and hospitalization is important.

3. Neglected hydrocephalus: It can commonly lead to motor weakness and spasticity. Presence of large head with patent fontanel and dilated scalp veins are the classic features. CT scan of the head is important for diagnosis and for differentiation from other causes of progressive head enlargement especially some types of leukodystrophy as Canavan disease and Alexander disease.

4. Leukodystrophies: These are a group of inherited diseases characterized by degeneration of the white matter of the brain. They differ in inheritance, age of onset, clinical presentation and rate of progression. Clinical presentations in infancy include hypotonia (kinky hair disease), spasticity (Krabbe disease), progressive macrocephaly (Canavan disease and Alexander disease) and nystagmus and head nodding (Pelizaeus-Merzbacher disease). Metachromatic leukodystrophy and adrenoleukodystrophy usually present in early and late childhood respectively. *CT scan of the head* is very useful in demonstrating degeneration of the white matter and should be made in any of the above clinical presentations.

Leukodystrophies

Disease	Inheritance	Onset	Clinical presentation
Kinky hair disease (Menkes disease)	XL	Infancy	Hypotonia, seizures Kinky hair
Krabbe disease (Globoid leukodystrophy)	AR	Infancy	Spasticity, Seizures
Canavan disease (Spongy degeneration)	AR	Infancy	Macrocephaly
Alexander disease	AR	Infancy	Macrocephaly
Pelizaeus- Merzbacher disease	XL	Infancy	Nystagmus and head nodding
Metachromatic leuko-dystrophy) (MLD)	AR	Early childhood	Hypotonia Slow progression over years
Adrenoleukodystrophy	XL	Late childhood	Academic deterioration Hypoadrenalism

- **Neonatal adrenoleukodystrophy** presents with severe hypotonia in neonatal period.

7. Progressive Motor Weakness

Brain causes	Spinal cord causes	Neuromuscular causes
Brain tumors Degenerative brain diseases	Spinal cord tumors Pott's disease	Spinal muscular atrophy Muscular dystrophies Myopathies

Gradual and progressive motor weakness is caused by either expanding tumors or degenerative diseases. Progression can be rapid over weeks as in tumors or slow over several months or years as in degenerative diseases. Loss of previously acquired motor skills can be symmetric or asymmetric and isolated or associated with other neurological findings.

- What is the level of dysfunction?
- What is the cause?

1. *What is the level of dysfunction?*

The level of dysfunction can be determined by considering the type of motor weakness (spastic or flaccid) and the associated neurological signs.

1. In brain dysfunction, motor weakness is usually ***spastic*** (with hyper-reflexia and positive Babiniski sign) and may be symmetric or asymmetric. Other neurological signs as cranial nerve palsy, increased intracranial pressure (morning headache, morning vomiting and blurred vision), ataxia and/or convulsions are commonly present.

2. In spinal cord dysfunction, motor weakness is usually ***spastic*** (with hyper-reflexia and positive Babiniski sign) and may be also symmetric or asymmetric. Other neurological signs as sensory loss (with sensory level on the trunk) and autonomic dysfunction (as urinary retention and stool incontinence) are usually present.

3. In neuromuscular dysfunction, motor weakness is always ***flaccid*** (with hyporeflexia) and symmetric. Other neurological manifestations are usually absent apart from mild mental retardation is some diseases as Duchenne muscular dystrophy.

2. *What is the cause?*

Although the cause can be clinically suggested in most cases, some investigations are necessary to confirm the diagnosis and to differentiate between conditions presenting with similar findings. Investigations should be individualized according to the most likely clinical diagnosis.

Possible investigations in progressive motor weakness

Suspected brain disease

- CT scan of the head or MRI: In ALL cases.
- Brain biopsy: May be considered in degenerative brain diseases.

Suspected spinal cord disease

- Myelography.
- CT scan of the spine or MRI.

Suspected neuromuscular disease

- Creatine phosphokinase (CPK).
- Nerve conduction velocity.
- Electromyography (EMG).
- Muscle biopsy.
- Investigations of endocrine myopathy as hypothyroidism, hyperparathyroidism, hyperaldosteronism (Conn's syndrome) and Cushing syndrome may be considered.

A) BRAIN CAUSES

1. Brain tumors: It should be considered when motor weakness is associated with increased intracranial pressure, convulsions, ataxia and/or cranial nerve palsies. CT scan of the head is essential for diagnosis and localization and for differentiation from degenerative brain diseases (see common malignancies and CT scan in Pediatrics).

2. Degenerative brain diseases: They should be considered in case of gradual deterioration of motor and intellectual functions. CT scan of the head can differentiate between degeneration of the gray and white matter. Brain biopsy is important for precise diagnosis.

a) ***Degenerative diseases of the gray matter*** usually present with initial deterioration of intellectual functions. Convulsions and blindness are common. Motor deterioration occurs in advanced cases. These diseases can be *storage diseases* (as infantile Gaucher, Tay Sack's disease) or *nonstorage* (as Alpers disease, Leigh's disease).

b) ***Degenerative diseases of the white matter*** usually present with initial deterioration of motor functions. They can be classified as *leukodystrophies* (see spastic infant) or *demyelinating diseases* (as multiple sclerosis and subacute sclerosing panencephalitis).

B) SPINAL CORD CAUSES

1. Spinal cord tumors: These tumors can be *intramedullary* (as astrocytoma and ependymoma), *extramedullary intradural* (as neurofibroma and meningioma) or *extramedullary extradural* (as neuroblastoma, leukemia and lymphoma). Progressive motor weakness (symmetric or asymmetric), gait disturbance and back pain are the most common initial presentations. Sensory loss with sensory level on the trunk and autonomic disturbance as urinary retention are common. CT scan of the spine or MRI are the most reliable methods for diagnosis.

2. Pott's disease of the spine: Tuberculosis of the spine with the resultant granulation and destruction can lead to spinal cord compression and motor weakness. Neurological manifestations are similar to those of spinal cord tumors. Spinal deformity as kyphosis with angulation is common. Other manifestations suggesting tuberculosis as chronic pulmonary disease and lymphadenopathy may be also present. Plain x-ray of the spine is useful in most cases, but CT scan or MRI are more reliable. Investigations should also include tuberculin test, ESR and chest x-ray.

C) NEUROMUSCULAR CAUSES

1. Spinal muscular atrophy (SMA): This autosomal recessive degenerative disease of the anterior horn cells has 3 forms: ***type 1*** (Severe infantile form or Werdnig-Hoffmann disease), ***type 2*** (late infantile form) and ***type 3*** (juvenile form or Kugelberg-Welander disease). Type 1 presents at birth or early infancy as a floppy infant. It is rapidly progressive as most cases die during the first year or two. Type 2 presents in late infancy with progressive motor weakness while type 3, which is a mild disease, starts in childhood. In all forms, weakness is flaccid and is purely motor. Tongue fasciculations is a specific clinical sign, which is always present. Fasciculations may be also observed in deltoids, biceps brachii and quadriceps femoris. Diagnosis is confirmed by electromyography (which show a vibrillation potentials and other signs of denervation of muscles) and muscle biopsy (characteristic changes). Nerve conduction velocity is normal and CPK is normal or mildly elevated.

2. Duchenne muscular dystrophy: It is commonest cause of chronic progressive motor weakness in children. It is an x-linked disease appearing only in males with an onset of illness during the first 5 years and usually after infancy. The main characteristic features are:

- *Weakness of shoulder girdle muscles:* The boy becomes unable to raise his arm above his head or to comb his hair. Slipping sign is positive (on trying to lift the child from the axillae, he slips through the examiner's hands).
- *Weakness of pelvic girdle muscles:* The boy has a waddling unsteady gait. Difficulty in climbing stairs and in rising from the floor is evident. Gower's sign is positive (the boy rises from the floor by climbing up his legs).
- *Pseudohypertrophy of calf muscles:* It is the most characteristic feature and it is usually associated with wasting of thigh muscles. Tongue and muscles of upper limbs may also show a pseudohypertrophy.
- *Other features:* Mild degree of mental retardation is usually present and cardio-myopathy is a constant feature and may be the cause of death.
- *The course* is gradually progressive and most patients become unable to walk at the age of 12 years. *Death* usually occurs during the next 5 years due to respiratory failure or severe congestive heart failure.
- *Confirmatory investigations:* Serum creatine phosphokinase is greatly elevated to thousands (normal level is below 60 units/liter). EMG shows nonspecific myopathic changes. Muscles biopsy is characteristic and diagnostic.

• The disease should be differentiated from other muscular dystrophies especially *Becker muscular dystrophy*. It is also an x-linked disease but with a later onset (in late childhood) and slower progressive course. Patients usually die in the third decade and occasionally in the fourth. Other muscular dystrophies should be also considered.

Muscular dystrophies

Disease	Onset	Remarks
Sex-linked diseases		
Duchenne muscular dystrophy	Early childhood	Commonest (1/3600)
Becker muscular dystrophy	Late childhood	Slow progression
Emry Dreifuss muscular dystrophy	Late childhood	Scapuloperoneal and joint contractures
Autosomal dominant diseases		
Myotonic dystrophy	Early childhood	Distal weakness
Fasioscapulohumeral muscular dystrophy	Early childhood	Asymmetry is common
Ocular muscular dystrophy	Early childhood	Ophthalmoplegia
Autosomal recessive diseases		
Congenital muscular dystrophy	Infancy	Floppy infant
Childhood muscular dystrophy	Early childhood	No hypertrophy
Limb girdle muscular dystrophy	Late childhood	No hypertrophy

• **Muscle biopsy** is essential for diagnosis

3. Endocrine and metabolic myopathies: ***Endocrinal diseases*** with progressive motor weakness include longstanding untreated hypothyroidism (Debre-Semelainge syndrome), hyperthyroidism, hyperparathyroidism and Cushing syndrome. ***Metabolic myopathies*** include glycogenosis type II (Pompe disease) and disorders of metabolism as systemic carnitine deficiency (onset in early childhood) and muscle carnitine deficiency (onset in late childhood).

Myositis is not included among the causes of progressive motor weakness because muscle pain and tenderness (and not motor weakness) is the most striking feature. ***Transient myositis*** is common with viral diseases. ***Chronic myositis*** occurs in systemic lupus erythematosus and in parasitic infiltration of muscles as in Trichinella spiralis and bilharziasis.

8. Movement Disorders

Ataxia	Chorea
Acute ataxia	**Acute chorea**
Acute cerebellar ataxia (viral)	Rheumatic chorea
Bacterial ataxia	Acute infections
Toxic ataxia	Toxic chorea
Traumatic hemorrhage	Hypernatremic dehydration
Brain tumours	Brain tumors
Familial paroxysmal ataxia	Familial paroxysmal choreoathetosis
Chronic ataxia	**Chronic chorea**
Ataxic cerebral palsy	Extrapyramidal cerebral palsy
Brain tumours	Brain tumors
Heredodegenerative ataxias	Heredodegenerative Chorea
Abetalipoproteinemia	Huntigton's chorea
Ataxia telengiectasia	Wilson disease
Friedreich ataxia	Lesch-Nyhan syndrome
Several other diseases	Several other diseases

Other abnormal movements are athetosis, dystonia, tics and tremors

Movement disorders in children include several conditions that may be present as isolated disorders or in different combinations. These disorders are commonly acute and transient but they may be also chronic with nonprogressive or progressive course.

- **Ataxia** is characterized by ***incoordination*** of postural tone and gait (truncal ataxia) and of skilled movements that are involved in hand movements and speech (volitional ataxia or limb ataxia). It is mostly related to a *cerebellar disease*.

- **Chorea** and other disorders (athetosis, dystonia, tics and tremors) are characterized by the presence of repetitive ***involuntary movements*** and are related to an extrapyramidal disorder mostly of the *basal ganglia*.

Although the diagnosis is mostly based on clinical findings, CT scan of the head is very useful in localization and identification of the nature of the lesion.

Value of CT scan of the head in movement disorders

Congenital anomalies: As agenesis of cerebellar vermis, Chiari malformation, encephalocele.
Infections: As in acute cerebellar ataxia (virus cerebellaritis).
Intracranial hemorrhage: Especially in the brainstem or cerebellum.
Brain tumors of posterior fossa.
Degenerative diseases.

A) ATAXIAS

The cerebellum is the coordinator of the postural tone and gait and of the skilled movements. It has a 3 parts that perform a computing function:

1. Archicerebellum (vestibular cerebellum): It is responsible for equilibrium.
2. Palaeocerebellum (spinal cerebellum): It is responsible for postural tone and gait.
3. Neocerebellum (90% of cerebellar surface): It is responsible for coordination of skilled movements forming a feedback loop with the cerebral cortex.

Ataxia results from a disease of the cerebellum itself or from interruption of its input (afferent fibres) or output (efferent fibres) connections. The afferent fibers are 40 times more than the efferent fibres. In other words, ataxia can be:

1. Cerebellar ataxia: Due to a cerebellar disease. It is the most common.
2. Sensory ataxia: Due to interruption of afferent spinocerebellar tracts.
3. Vestibular ataxia: Due to interruption of afferent vestibulocerebellar tracts.

- How to diagnose ataxia?
- What is the type?
- What is the cause?

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1. How to diagnose ataxia?

Clinical diagnosis of ataxia depends on the following signs:

1. Ataxic gait (truncal ataxia): It is a wide base unsteady gait with staggering and movements in any direction (drunken gait). Compensatory balancing movements of the upper limbs to avoid falling are characteristic (the upper limbs are held sideaways as a balancing poles). Walking is slower than normal. The child cannot stand on one leg and if he is standing still there is a constant adjustment of posture.

2. Incoordination of skilled movements (volitional ataxia): It includes the skilled movements of the limbs and the speech:

a) Limb ataxia: The movements of the limbs become clumsy with poor adjustment of force, speed and direction. *Clinical manifestations* of poor adjustment are: (1) intention tremors, (2) decomposition of movements, (3) dysmetria and pastpointing due to difficulty in judging distance. In cooperative older children some *clinical tests* can be used to demonstrate the poor adjustment, (1) finger to nose or finger to finger test, (2) inability to fasten or unfasten buttons, (3) inability to perform rapid alternating pronation and supination (dysdiadochokinesia).

b) Stacatto speech: The speech is interrupted with unclear words. This is only evident in older children.

c) Nystagmus: It is common in acquired ataxias but usually absent in congenital lesions. It is mainly horizontal in direction.

3. Hypotonia: A mild degree of hypotonia and hyporeflexia is usually present. Occasionally, hypotonia is severe and simulating acute paralysis. In infants, severe hypotonia (floppy infant) is the only evident finding because other manifestations as ataxic gait and limb ataxia cannot be tested in infants.

2. *What is the type?*

Cerebellar ataxia is by far the most common type. Clinical manifestations of ataxia are evident (truncal, volitional and hypotonia).

Sensory ataxia is rare in children because lesions causing selective loss of deep sensations are rare. The main manifestations are intention tremors and ataxic gait *only* when the patient closes his eyes.

Vestibular ataxia occurs with acute labyrinthitis complicating otitis media. In young children it cannot be clinically differentiated from acute cerebellar ataxia (virus cerebellaritis) as in both conditions truncal ataxia is the most evident feature. In older children, vertigo is evident. Incoordination of skilled movements is usually absent.

3. *What is the cause?*

(a) Acute ataxias

1. Acute cerebellar ataxia (virus cerebellaritis): It is the most common cause of acute ataxias, which mostly occurs between the ages of 1-5 years. It usually occurs 2 - 3 weeks after a viral illness as chickenpox, enteroviruses and influenza viruses (parainfectious demyelination). It starts suddenly in an otherwise well child. Truncal ataxia and hypotonia are the most evident features. Intention tremors and horizontal nystagmus may be also present. There is no fever, meningeal irritation or increased intracranial pressure. Diagnosis should be only made after exclusion of other acute ataxias. Prognosis for complete recovery is excellent. Most cases recover in a few weeks or up to 2 months.

2. Bacterial ataxia: Cerebellar abscess, acute labyrinthitis following middle ear infection and bacterial meningitis are the main causes. The possibility should be considered when ataxia is associated with fever, headache, vomiting, intense vertigo or meningeal irritation. CT scan of the head and CSF examination are indicated in these situations. Occasionally, diphtheria and pertussis may be complicated by acute ataxia.

3. Toxic ataxia: Antiepileptics (especially phenytoin overdosage), antihistamines and piperazine (antihelmintic drug) are important causes. Exogenous toxins as lead encephalopathy, alcohol ingestion and glue sniffing should be also in mind.

4. Traumatic hemorrhage: Head injury with secondary brainstem hemorrhage is a common cause of ataxia, which may persist for 6 months or more. Cerebellar hemorrhage may be also responsible.

5. Brain tumors: As ataxia is one of the main presentations of brain tumors, the possibility should be always excluded in every case of ataxia in a child whether acute or gradual. Cerebellar medulloblastoma or hemorrhage into a benign astrocytoma usually present with acute ataxia. Other neurological manifestations especially increased intracranial pressure and cranial nerve palsies may be also present. CT scan of the head is essential for diagnosis.

6. Familial paroxysmal ataxia: It is an autosomal dominant disease characterized by recurrent episodes of acute ataxia. The illness usually starts as early as 2 years and increases in severity in late childhood. Each episode lasts from several days to a month and clears spontaneously. In adults, the episodes are short and each one lasts only for 2 days.

(b) Chronic ataxias

Static or nonprogressive chronic ataxia is mostly due to ataxic cerebral palsy. Brain tumours and heredodegenerative diseases are the causes of progressive chronic ataxias.

1. Ataxic cerebral palsy: The manifestations of ataxia do not appear before the age of 1 year. Truncal ataxia and limb ataxia are present but nystagmus is usually absent. The ataxia is characteristically nonprogressive which is an important differentiating point from heredodegenerative diseases. CT scan of the head may reveal cerebellar anomalies as agenesis of cerebellar vermis.

2. Brain tumors: Gradual and progressive ataxia in a child should always raise the possibility of brain tumors. CT scan of the head is essential for diagnosis or exclusion.

3. Heredodegenerative ataxias: A long list of more than 30 rare diseases is present and usually makes a difficult diagnostic problem even in specialized units. The most important of these disorders are:

a) ***Abetalipoprotinemia:*** It is characterized by *malabsorption* in infancy and *progressive ataxia* in childhood. A blood smear shows *acanthocytosis* and fundus examination reveals *retinitis pigmentosa.*

b) ***Ataxia telangiectasia:*** It is characterized by *progressive ataxia* starting in early childhood. *Telangiectasia* of bulbar conjunctiva, nasal bridge, ears and may be extremities appear at 5 - 6 years. The most important characteristic feature is the *inability to move the eyes* on command. *Immunodeficiency* is common as evidenced by absent tonsillar tissue, recurrent infections and decreased secretory IgA and IgG. There is a great risk of developing *malignancies* especially lymphoma, leukemia and brain tumors.

c) ***Friedreich ataxia:*** It is characterized by a slowly progressive ataxia starting in late childhood. The characteristic *neurological triad* is ataxia, positive Babiniski sign (pyramidal lesion) and lost ankle jerk (peripheral neuritis). Other clinical findings include *cardiomegaly* and *pes cavus.*

d) ***Other causes*** include metachromatic leukodystrophy, Von Hippel Lindau disease, Refsum disease and argininosuccinic acidemia.

B) CHOREA

Chorea is an extrapyramidal disease of the basal ganglia characterized by rapid, jerky, purposeless and nonrhythmic involuntary movements involving mainly the muscles of the face, trunk and distal extremities.

(a) Acute chorea

1. Rheumatic chorea (Sydenham chorea): It is the most common form of acquired chorea in children and is the only neurological manifestation of rheumatic fever. The condition occurs mainly in school age children and females are often more affected. The illness usually occurs several weeks or several months after streptococcal pharyngitis, and usually without other manifestations of rheumatic fever. The onset can be abrupt but more commonly it is insidious. Clinical diagnosis depends on the following signs:

a) Choreic movements: They are rapid, jerky, purposeless and nonrhythmic movements involving mainly the muscles of the face, trunk and distal extremities. Movements are aggravated by emotional stress and disappear during sleep. The condition may be misinterpreted as voluntary movements to irritate parents or teachers.

b) Emotional lability: The patient often appears nervous and may show sudden outbursts of crying without an apparent cause.

c) Hypotonia: The degree of hypotonia is variable. The child usually becomes unable to eat independently and he frequently drops objects. In severe cases, it interferes with walking and stimulates acute paralysis.

d) Typical signs: Several specific signs can be elicited

(i) Darting tongue: The tongue cannot be protruded for a longer than a few seconds.
(ii) Choreic hand: The extended hands show wrist flexion and fingers extension.
(iii) Pronator sign: The arm and palm turn out when held above the head.
(iv) Milk maid's grip: With shaking hands, relaxing and tightening handshake occurs.

- Associated rheumatic heart disease is present in one third of cases.
- The course is benign in most cases. Initially, symptoms usually increase in severity during the first few weeks then it gradually subsides over several weeks or few months. In some cases, the illness may persist as long as 1-2 years. Recurrences are common.
- The evidence of preceding streptococcal infection is commonly lacking. Throat culture is frequently negative and ASO titer is commonly normal.

2. Other causes of acute chorea: *Acute infections* as diphtheria or pertussis may be accompanied with chorea. *Toxic chorea* may occur with isoniazid or reserpine toxicity. Severe *hypernatremic dehydration* may be also followed with chorea. Although uncommon, *brain tumors* may lead to chorea. *Familial paroxysmal chorea* is a rare autosomal dominant disease characterized by recurrent episodes of very transient choreoathetosis (lasting for a few seconds to several minutes). The condition should not be confused with epilepsy.

b) Chronic chorea

1. Extrapyramidal cerebral palsy: It commonly follows kernicterus (post-icteric choreoathetosis). It is characterized by an early onset, in late infancy or early childhood, and nonprogressive course.

2. Brain tumors: Recent chorea in a child especially when associated with other neurological signs as cranial nerve palsies or increased intracranial pressure should suggest brain tumors. CT scan is essential for diagnosis.

3. Heredodegenerative chorea: Several inherited conditions are accompanied with chorea but all are rare.

a) ***Huntington chorea:*** It is an autosomal dominant disease characterized by progressive chorea, dystonia, rigidity, mental retardation and epilepsy. It is a disease of adulthood, which is very rare in children.

b) ***Wilson disease:*** It is an autosomal recessive disease characterized by abnormal deposition of copper in the liver and CNS. It should be considered in any child above 8 years presenting with a recent neurological disease. Laboratory diagnosis depends on a high serum copper, low serum ceruloplasmin and high urinary excretion of copper (see also hepatosplenomegaly).

c) ***Lesch-Nyhan syndrome:*** It is an x-linked disease of purine metabolism characterized by choreoathetosis and self-mutilation (uncontrollable aggressive behavior directed against the patient himself). Spasticity and mental retardation are also present and nephropathy (due to raised uric acid) is usually the cause of death. The plasma uric acid is raised.

d) ***Chorea*** may accompany other conditions as ataxia telangiectasia.

C) OTHER ABNORMAL MOVEMENTS

Chorea should not be confused with other abnormal movements:

1. Athetosis: It is a slow rhythmic *writing movements* of distal parts of extremities. It commonly occurs with chorea (choreoathetosis).

2. Dystonia: It is a slow *twisting movements* of proximal parts of extremities, trunk and face with slow relaxation of muscles.

3. Tics: It is a rapid repetitive *stereotyped movements* usually involving areas supplied by cranial nerves as eye muscles, facial muscles, neck and shoulders. They do not interfere with normal activities but they get worse with emotional stress. They are mainly psychological and transient lasting from few weeks to several months.

4. Tremors: It is a rapid *very rhythmic movements* mainly involving the hands. It can be *static* (as in basal ganglia disorders) or *kinetic* and appearing only during movements (as with intention tremors of ataxia). *Flapping tremors* may be seen in hepatic failure. *Physiological tremors* occur with severe anxiety and with overdosage of beta agonists as salbutamol (ventolin).

9. Neurocutaneous Syndromes

Autosomal dominant	Autosomal recessive	Nongenetic (sporadic)
Neurofibromatosis Tuberous sclerosis Von-Hipple-Lindau	Ataxia telengiectasia Sjogren-Larsson disease	Sturge-Weber disease Linear nevus syndrome
Incontinentia pigmenti is an **x-linked dominant disease**		

Neurocutaneous syndromes (or neurodermatoses) are a group of disorders characterized by involvement of the CNS and skin and are associated with a high risk of developing tumors. The most common of these disorders are neurofibromatosis (1/4000), tuberus sclerosis (1/30000) and Sturge-Weber disease (1/50000). Other disorders are rare.

1. Neurofibromatosis (NF): It has two types (type 1 and type 2). ***Type 1*** account for 90% of cases and it has several manifestations while ***type 2*** is only present in 10% of cases and is mainly characterized by bilateral acoustic neuroma. The main characteristic features of type 1 are:

a) Cutaneous manifestations: *Cafe-au-lait spots* are the most characteristic feature of the disease as they are present in 100% of cases. They are present at birth with tendency to increase in size, number and pigmentation during the first few years of life. Presence of more than 5 spots greater than 5 mm in diameter is diagnostic. *Neurofibromas* of the skin and subcutaneous tissues usually appear in late childhood. Skin lesions appear as a soft pedunculated masses while subcutaneous lesions appear as a soft subcutaneous nodules attached along peripheral nerves or blood vessels. Plexiform neurofibroma is a large infiltrative tumour causing considerable disfigurement.

b) Neurological manifestations: Learning and speech difficulties are common. Epilepsy and intellectual deficits may also occur. Occlusion of cerebral vessels by neurofibromatosis may lead to hemiparesis.

c) Tumors: *Brain tumors* (optic glioma, meningioma, neurofibroma or astrocytoma) are common and should be considered. The incidence of *other malignancies* (as leukemia, neuroblastoma, Wilms tumor and rhabdomyosarcoma) is also high. Tumors are the principal risk and the main cause of death.

d) Other features: *Skeletal lesions* as kyphoscoliosis, bowlegs, long bone cysts and pulsating exophthalmos are common. *Ocular lesions* especially iris Lisch nodules are present in 90% of cases and can be demonstrated by slit lamp examination. Glaucoma may also occur.

2. Tuberous sclerosis (TS): It is a multisystem disease with a wide range of clinical presentations and severity. The main characteristic features are:

a) Cutaneous manifestations: Hypopigmented macules on the trunk and limbs are present at birth in almost all cases. They are oval or irregular and ranging from few mm to several cms. *Sebaceous adenomas* are the most characteristic lesion that usually appears at 4 - 6 years. They are small bright red or brownish nodules on the nose and cheeks (butterfly distribution), which may be confused with acne. *Shagreen patches* are a slightly raised indurated areas mainly located in lumbosacral region (see Short Atlas in Pediatrics).

b) Neurological manifestations: Epilepsy is present in 90% of cases and it may be resistant to therapy. Mental retardation is present in 60% of cases and ranging from mild to severe. Behavioural disorders as hyperactivity and destructiveness are common.

c) Tumors: Rhabdomyoma of the heart and renal tumors are the most common and can lead to congestive heart failure or renal failure. Brain tumors are less common.

- Plain skull x-ray may demonstrate periventricular calcification (see Basic Pediatric Radiology). CT scan of the head can clearly demonstrate these calcified tubers.

3. Sturge-Weber disease: It is a nongenetic (sporadic) disease. The main characteristic features are:

a) Cutaneous manifestations: Unilateral facial nevus involving the upper face and eyelid is the most characteristic feature (see Short Atlas in Pediatrics). It is usually present at birth (not all children with facial nevus have Sturge-Weber disease).

b) Neurological manifestations: Unilateral convulsions and hemiparesis of the other side are common. Learning difficulties or mild retardation may occur in late childhood.

c) Tumors: Angioma of cerebral cortex or hemangioma of choroid may occur.

- Skull x-ray shows the characteristic serpentine calcification of the occipitoparietal region (see Basic Pediatric Radiology). CT scan of the head is more reliable for diagnosis.

Other neurocutaneous syndromes

Syndrome	Cutaneous	Neurological	Tumors
Von-Hippel-Lindau	Retinal angioma	Ataxia	Cerebellar
Ataxia telangiectasia	Telangiectasia	Ataxia	Lymphomas
Refsum disease	Ichthyosis	Ataxia	—
Sjogren Larsson	Ichthyosis	Diplegia	—
Incontinentia pigmenti	Pigmentation	Epilepsy, MR	Eye
Linear nevus syndrome	Forehead nevus	Epilepsy, MR	—

6

Cardiovascular System

- Cardiovascular Examination
1. Congenital Heart Disease.
2. Acute Rheumatic Fever.
3. Chronic Rheumatic Heart Disease.
4. Cardiac Infections.
5. Cardiomyopathy.
6. Congestive Heart Failure.
7. Circulatory Failure (Shock).
8. Cardiac Arrhythmias.

Cardiovascular examination

Extracardiac examination	Cardiac examination
Appearance Peripheral perfusion Vital signs (HR, RR, BP) Arterial pulsations	Inspection Palpation Percussion Auscultation
Useful for detection of: • Cyanosis • Shock • Congestive heart failure • Abnormal pulsations	Useful for detection of: • Cardiac enlargement • Cardiac murmurs • Abnormal heart sounds • Paricardial rub

Evaluation of the cardiovascular system should include two essential steps; extracardiac and cardiac examination.

A) EXTRACARDIAC EXAMINATION

It is an extremely important initial step and actually more important than the cardiac examination because abnormalities detected are mostly serious and life-threatening necessitating urgent management. Examination should be directed for detection of the following

1. Cyanosis: *Acute* cyanosis with respiratory distress is observed in severe respiratory or congestive heart failure. *Chronic* cyanosis without or with mild respiratory distress is mostly due to a congenital cyanotic heart disease. Cyanosis of cardiac origin in characteristically becomes more evident with crying or exertion (see cyanotic CHD).

2. Shock (circulatory failure): It mainly occurs in severe hypovolemia, severe septicemia and severe congestive heart failure. The main manifestations are poor peripheral perfusion, tachycardia and hypotension (see shock).

3. Congestive heart failure: In *acute* failure, the cardinal triad is tachycardia, tachypnea and enlarged tender liver. In *chronic* failure, exertional dyspnea is present with or without other features of systemic congestion as engorged neck veins, hepatomegaly and oedema of lower limbs (see congestive heart failure).

4. Abnormal pulsations: Palpation of superficial pulsations in upper and lower limbs is very important for detection of *coarcration of the aorta*. Weak or absent pulsations in lower limbs is very suggestive of coarctation. In this condition, an additional simple confirmatory finding is the presence of hot hands and cold feet. Other abnormal findings include *water hummer pulse* and *arrhythmias* especially premature beats and atrial fibrillation.

B) CARDIAC EXAMINATION

It includes inspection (precordial bulge, apex beat, visible pulsations), palpation (apex beat, palpable thrills) and auscultation (murmurs, heart sounds and abnormal sounds as pericardial rub). *Percussion is almost obsolete* in pediatric cardiology because it cannot easily detect cardiac enlargement in young patients and, it cannot differentiate between right and left ventricular hypertrophy. Cardiac examination should be directed for detection of:

1. Cardiac enlargement: Manifestations vary according to the degree:

a) Mild cardiomegaly is difficult to detect clinically.

b) Moderate cardiomegaly can be detected clinically by inspection and palpations:

- *With right ventricular hyperrophy,* visible left parasternal and epigastric pulsations are present. The apex beat is shifted outwards and the maximal impulse is felt in the left parasternal area.
- *With left ventricular hypertrophy,* visible apical pulsations are present. The apex is shifted outwards and downwards with maximal impulse over the displaced apex.
- *With combined ventricular hypertrophy,* both findings are present.

c) Huge cardiomegaly is associated with visible precordial bulge.

2. Cardiac murmurs: The comment on cardiac murmurs should include: (1) duration (systolic, diastotic or continuous), (2) intensity (faint or loud. Grades from 1 to 6), (3) character (soft, harsh or rumbling), (4) location (area of maximal intensity) and (5) Propagation. Loud organic murmurs are associated with palpable thrills. Murmurs can be ***innocent*** (physiological) or ***pathological*** denoting valvular, vascular or shunt lesions. Clinical diagnosis of the underlying cardiac lesion depends mainly on the duration and location of the murmurs.

3. Abnormal heart sounds: ***Muffled sounds*** with tachycardia suggest the diagnosis of myocarditis. Gallop rhythm and cardiomegaly are additional evidences. ***Weak distant sounds*** with quiet precordium suggest the diagnosis of pericardial effusion. ***Abnormalities in second sound*** over the pulmonary area provide a useful differentiating point especially in noncyanotic congenital heart diseases.

4. Pericarclial rub: It is a friction sound heard over the heart in case of pericarditis. It is not related to cardiac areas or to cardiac cycle.

In every cardiac patient, some **investigations** are always necessary for proper assessment of the cardiac size and the underlying cardiac disease. These investigations include chest x-ray, electrocardiogram (ECG) and echocardiography.

1. Congenital Heart Disease

Cyanotic congenital heart disease (20% of cases)	
With decreased pulmonary blood flow (Oligemic lung fields)	**With increased pulmonary blood flow (Plethoric lung fields)**
With right ventricular hypertrophy Fallot's tetralogy Transposition with pulmonary stenosis Double outlet RV with PS **With left ventricular hypertrophy** Pulmonary atresia Tricuspid atresia	**With right ventricular hypertrophy** Hypoplastic left heart syndrome Transposition of great arteries Total anomalous pulmonary venous return **With right, left or both VH** Truncus arteriosus Single ventricle
Ebstein anomaly is characterized by huge right atrial enlargement	

Noncyanotic congenital heart disease (80% of cases)	
With normal pulmonary blood flow	**With increased pulmonary blood flow**
Valvular lesions Pulmonary stenosis(PS) Aortic stenosis (AS) Mitral regurgitation (MR) Tricuspid regurgitation (TR) **Vascular lesions** Coarctation of aorta Coronary anomalies **Endomyocardial disease** Endocardial fibroelastosis Metabolic diseases	**Common shunt lesions** Ventricular septal defect (VSD) Atrial septal defect (ASD) Patent ductus arteriosus (PDA) **Uncommon lesions** Aorticopulmonary septal defect Coronary arteriovenous fistula Partial anomalous pulmonary venous return

Congenital heart diseases are a common pediatric problem. The general incidence is about 6/1000. Males and females are equally affected. They are considered as genetic diseases of *multifactorial inheritance* with a recurrence rate about 5 %. Approximately 30% of cases are associated with syndromes and 10% with extracardiac malformations.

• **Cyanotic congenital heart diseases** account for 20% of cases. Fallot's tetralogy (10%) and transposition of great arteries (5%) are the most common. In this group, accurate clinical diagnosis can *never* be made and investigations as chest x-ray, ECG

and echocardiography are essential for diagnosis. Cardiac catheterization is also necessary before corrective surgery. Prognosis is generally bad unless a corrective surgery is performed early.

• **Noncyanotic congenital heart diseases** accounts for 80% of cases. Ventricular septal defect (25%) is by far the most common followed by ASD, PDA, PS, AS and coarctation (10% for each). In this group, clinical diagnosis *can* be made and confirmed by simple investigations. In many cases, prognosis is generally good even without a corrective surgery.

A) CYANOTIC CONGENITAL HEART DISEASE

In this group, ***chronic central cyanosis*** is the main presentation. Clinical evaluation is useful to put some possibilities forward but it can never provide an accurate diagnosis. Chest x-ray, ECG and echocardiography are essential.

- How to diagnose central cyanosis?
- What is the onset of cyanosis?
- What is the condition of pulmonary blood flow?
- Which ventricle is enlarged?
- What is the diagnosis?

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1. *How to diagnose central cyanosis?*

Central cyanosis is the bluish discoloration of the lips, tongue and mucous membranes of oral cavity and fingernails.

• ***Degree of cyanosis:*** In mild or early cases, central cyanosis is mainly *exertional* and appears only during crying, suckling or exertion. In established cases, cyanosis is *constant* and becomes deeper with exertion. In *longstanding* cases (usually above 6 months), growth failure and clubbing of fingers occur.

• ***Effects of cyanosis:*** Because of compensatory polycythemia and hemoconcentration, murmurs over the heart may disappear *(murmurless cyanotic CHD)* and *anemia* may be masked. *Venous thrombosis* leading to hemiplegia or brain abscess may occur.

• ***Laboratory confirmation:*** The clinical diagnosis of cyanosis can be confirmed in doubtful cases by 2 tests:

(i) Hemoglobin and hematorit value: Both are high due to polycythemia.
(ii) Arterial blood gases: Low PaO_2 (below 35 mm Hg) and oxygen saturation.

2. *What is the onset of cyanosis?*

The time at which cyanosis appears is useful is suggesting some possibilities:

• ***Early onset cyanosis*** (appearing at birth or within the first few days) suggests transposition of great arteries as the first possibility. Other 4 possibilities are pulmonary atresia, tricuspid atresia, hypoplastic left heart syndrome and total anomalous pulmonary

venous return. In this case, urgent diagnostic measures are essential because in transposition of great arteries infusion of prostaglandin E to keep the ductus patency is important. Ballon atrial septostomy (BAS) below the age of 2 weeks can be an alternative.

• ***Delayed onset cyanosis*** (cyanosis appearing at the age of 1-2 months) suggests Fallot's tetralogy as the first possibility. Other 4 possibilities are transposition with PS, double outlet right ventricle with PS, pulmonary stenosis with VSD and pseudotruncus (see below). These 4 conditions cannot be differentiated clinically or radiologically from Fallot's tetralogy. Echocardiography and demonstration of the origin of great vessels is essential for differentiation.

• ***Variable onset cyanosis:*** In truncus arteriosus, single ventricle and Ebstein anomaly cyanosis may appear at any time from birth to childhood, so these 3 conditions should be also considered in the above 2 groups. Cyanosis appearing in childhood should also suggest Eisenmenger syndrome with shunt reversal as in VSD and PDA.

3. What is the condition of pulmonary blood flow?

The condition of pulmonary blood flow can be assessed clinically and radiologically:

• ***Clinical assessment:*** With decreased pulmonary blood flow, hypercyanotic spells are common while congestive heart failure is unusual. With increased pulmonary blood flow, repeated chest infection and congestive heart failure are common.

• ***Radiological assessment:*** The lung field appearance is useful. With decreased pulmonary blood flow, lung field is oligemic while with increased blood flow, lung field is plethoric.

4. Which ventricle is enlarged?

Ventricular enlargement can be assessed clinically and by ECG.

• ***Clinical assessment:*** With right ventricular hypertrophy, the apical impulse is maximal over the left sternal border while with left ventricular hypertrophy the apical impulse is maximal over the apex.

• ***Electrocardiogram (ECG):*** With right ventricular hypertrophy R/S ratio is increased in V1and decreased in V6 while in left ventricular hypertrophy R/S ratio is decreased in V1 and increased in V6.

5. What is the diagnosis?

According to *pulmonary blood flow* and *ventricular hypertrophy,* cyanotic congenital heart diseases are classified into 2 groups and each group is divided into 2 subgroups (see above). In other words, with clinical assessment, chest-x-ray and ECG we can only reach a group diagnosis. ***Echocardiography*** is essential for accurate diagnosis.

It is important to remember that ***cardiac murmurs*** are not a useful differentiating point because murmurs may be variable in the same anomaly and they may disappear

due to hemoconcentration. In simple transposition, there are usually no murmurs while in other conditions, ejection systolic or continuous murmur is usually present.

It is also important to remember that ***heart shape and size*** may be only useful in longstanding cases. Examples of special configurations are: boot shaped heart (Fallot's tetralogy), egg shaped heart (transposition), and huge right atrium (Ebstein anomaly).

Complete examination for detection of associated syndromes or extracardiac anomalies is important. Neurological, morphological and skin examinations are particularly important. Exclusion of renal anomalies is also important.

Summary of the diagnostic approach of cyanotic congenital heart diseases

History

Onset of cyanosis.
History of hypercyanotic spells (decreased pulmonary blood flow).
History of repeated chest infection or congestive heart failure (increased pulmonary blood flow).

Examination

Apical impulse (ventricular hypertrophy).
Cardiac murmurs.
Complete examination for detection of associated anomalies.

Investigations

Hemoglobin, hematocrit and blood gases (for confirmation of cyanosis).
Chest x-ray (pulmonary blood flow, cardiac size and shape).
ECG (ventricular hypertrophy).
Echocardiography: Accurate diagnosis.
Cardiac catheterization: Before surgery.

1. Fallot's tetralogy: It is the commonest cyanotic congenital heart disease (10% of all and 50% of cyanotic group). It has 4 components: (1) Overriding aorta, (2) Pulmonary stenosis, (3) VSD and (4) Right ventricular hypertrophy (RVH).

- *Central cyanosis* usually appears at the age of 1- 2 months. In early cases, cyanosis is only exertional and appears during suckling or crying.
- *Hypercyanotic spells* are common. These attacks of deep cyanosis and respiratory distress are precipitated by crying, infections or iron deficiency anemia. Mild attacks (for minutes) are followed by weakness and sleep, while severe attacks (for hours) may progress to convulsions and unconsciousness.
- *Clubbing of the fingers* is usually not observed before the age of 1 year.
- Cardiac examination reveals *right ventricular hypertrophy* and ejection systolic or pansystotic murmur. The heart is not or only mildly enlarged.
- Heart x-ray shows *oligemic lung field* and boot shaped heart *(coeur en sabot)*.
- Echocardiography is essential for diagnosis and for differentiation from other conditions especially transposition with PS and double outlet right ventricle with PS.

Cardiac anomalies in Fallot's tetralogy and Fallot's-like conditions

Pulmonary stenosis	+	VSD	+ RVH	+	overiding aorta	=	Fallot's tetralogy.
Pulmonary stenosis	+	VSD	+ RVH	+	transposition of GA	=	Transposition with PS.
Pulmonary stenosis	+	VSD	+ RVH	+	double outlet RV	=	Double outlet RV with PS.
Pulmonary stenosis	+	VSD	+ RVH	+	Normal aortic root	=	PS with VSD.
Pulmonary atresia	+	VSD	+ RVH	+	Normal aortic root	=	Pseudotruncus.

2. Transposition of great arteries (TGA): ***Simple or isolated TGA*** is the second most common cyanotic congenital heart disease. In this condition, aorta arises from the right ventricle and pulmonary artery arises from the left ventricle. This results in 2 independent circuits, which cannot maintain life (one from aorta to right side of the heart and the other from pulmonary artery to left side of the heart). Life is maintained by a defect, which permits some mixture of blood. It is either foramen ovale or PDA.

- Central cyanosis and tachypnea *appear at birth* or during the first few days.
- Cardiac examination usually reveals *no murmurs.*
- Chest x-ray reveals *plethoric lung field* and may be *egg-shaped heart.*
- ECG shows *right ventricular hypertrophy.*
- Urgent diagnosis by echocardiography is essential. Urgent management includes measures that permit better mixing of blood. Prostaglandin E infusion (0.05-0.2 mcg/kg/minute) maintains ductal patency or reopens the closing ductus. Ballon atrial septostomy (BAS) allows atrial mixture of blood. The corrective surgery (arterial switch operation) is better to be done as early as possible.
- It is important to remember that transposition of great arteries can be ***associated with other cardiac anomalies.*** Transposition with VSD and PS gives a milder disease mimicking Fallot's tetralogy (see above). It can be also associated with pulmonary atresia, PDA or with overriding pulmonary artery (Taussig-Bing syndrome).
- Transposition of great arteries should be differentiated from other cyanotic congenital heart diseases especially those presenting at birth or in the first few days.

Cardiac anomalies in TGA and other causes of early onset cyanosis

Transposition of great arteries: Transposition + shunt (ASD, VSD or PDA).
Pulmonary atresia: Atresia of pulmonary valve and RV + shunt (ASD).
Tricuspid atresia: Atresia of tricuspid valve and RV + shunt (ASD).
Hypoplastic left heart syndrome: Hypoplasia of LV, aorta, mitral or aortic valves + shunt (ASD).
Total anomalous pulmonary venous return: Pulmonary veins return to the right atrium or one of its tributaries (i.e. wrong venous return) + shunt (ASD).
Truncus arteriosus: One vessel leaving the heart and giving rise to pulmonary arteries, aorta and coronaries + shunt (VSD).
Single ventricle: Absent interventricular septum, ± PS.
Ebstein anomaly: Huge right atrium + small right ventricle + shunt (ASD).

The onset of cyanosis in the last 3 conditions in variable (ranging from birth to childhood).

B) NONCYANOTIC CONGENITAL HEART DISEASE

In this group, there are 3 clinical presentations

1. Cardiac murmurs: Ejection systolic, pansystolic or continuous murmurs.
2. Disparity in pulsations and blood pressure: Coarctation of aorta.
3. Cardiomegaly and chronic congestive heart failure: Endomyocardial diseases.

It is also important to remember that ***complete examination*** is essential for detection of associated syndromes or extracardiac anomalies especially:

- Chromosomal diseases: Trisomies, deletions, Turner syndrome (coarctation).
- Metabolic diseases: Glycogenosis, mucopolysaccharidosis.
- Skeletal diseases: Ellis Van Creveld, Marfan syndrome.
- Hematological: Fanconi anemia, thrombocytopenia absent radius (TAR).
- Characteristic face: Noonan syndrome or pseudo-Turner (Turner-like features and PS) and William syndrome (idiopathic hypercalcemia, elfin face, mental retardation and supravalvular aortic stenosis).
- Associated malformations: Cleft lip and palate, hypospadius, cryptorchidism, hemivertebrae, meningomyelocele, hidden urinary anomalies.

1. Cardiac murmurs

When auscultation reveals a cardiac murmur, it is initially essential to differentiate between innocent and pathological murmurs.

- **Innocent (functional) murmurs** are common murmurs, which can be heard in up to 50% of normal children. They are a faint soft murmurs mostly ejection systolic (except venous hum which is a continuous murmur). They are usually changing in intensity with changes in the position and they are essentially not associated with any cardiac dysfunction. They differ in the age of appearance, site of maximal intensity and the origin.

Innocent murmurs

Murmur	Age	Site	Origin
Peripheral pulmonary stenosis	Newborn	Pulmonary area	Pulmonary artery
Vibratory (still's) murmur	3 – 8 years	LSB or apex	Unknown
Carotid bruit	3 – 8 years	Supraclavicular	Carotid artery
Venous hum	3 – 8 years	Infraclavicular	Jugular veins
Pulmonary flow murmur	6 –18 years	Pulmonary area	Pulmonary valve

LSB (left sternal border). All are ejection systolic except venous hum (continuous).

- **Pathological murmurs** are significant loud murmurs, which may be ejection systolic, pansystolic, continuous or diastolic. They are commonly associated with a thrill (palpable murmur) and cardiac dysfunction.

Clinical diagnosis of pathological murmurs depends on:

- Duration and site of maximal intensity of the murmur.
- Second heart sound: Normal, weak or loud, split or not.
- Ventricular hypertrophy: Right, left or both.

Laboratory confirmation of clinical diagnosis should include:

- Chest and heart x-ray: Pulmonary blood flow, cardiac size and shape.
- Electrocardiography (ECG): Ventricular hypertrophy.
- Echocardiography: Accurate diagnosis.

(a) Ejection systolic murmurs

1. Atrial septal defect (ASD): It is a common disease, which accounts for about 10% of all congenital heart diseases. The atrial defect can be *high* in the septum ***(sinus venosus defect),*** in the *midportion* ***(ostium secondum defect)*** or *low* in the septum primum ***(ostium primum defect, or endocardial cushion defect).*** Sinus venosus and ostium secondum defects are mostly asymptomatic in children and they are usually discovered on routine cardiac examination. Ostium primum defect and endocardial cushion defect (atrioventricular canal) are commonly associated with cardiomegaly and congestive heart failure in infancy.

- The ejection systolic murmur is maximally heard over the *pulmonary area.* It is usually not loud (grade I to II) and rarely accompanied by a thrill.
- The second sound over the pulmonary area is *widely split and fixed.* This is the most characteristic finding of the disease.
- Variable degree of *right ventricular hypertrophy* is usually present as evidenced by the left parasternal pulsations.
- Chest x-ray reveals enlarged pulmonary segment and RV. ECG reveals right ventricular hypertrophy and right axis deviation. Echocardiography demonstrates the defect.

2. Pulmonary stenosis (PS): It is a common disease, which accounts for about 8% of all congenital heart diseases. The condition is asymptomatic in most cases. However, severe to critical stenosis may cause exertional dyspnea, fatigability and exertional chest pain.

- The ejection systolic murmur is maximally heard over the *pulmonary area* (as in ASD). The murmur is usually louder (grade I to IV) and more significant than that of ASD. It is usually preceded by an ejection click. In severe cases, a palpable thrill is also present.
- The pulmonary component of the second sound is *weak or inaudible.*
- Variable degree of right ventricular hypertrophy is usually present according to the degree of stenosis.
- Chest x-ray reveals prominent pulmonary segment and variable RVH. ECG reveals RVH and right axis deviation. Echocardiography is diagnostic.

3. Aortic stenosis (AS): It is a common disease, which accounts for about 10% of all congenital heart diseases. Valvular stenosis is the commonest but supravalvular or subvalvular stenosis may occur. Supravalvular stenosis can be sporadic or associated with William syndrome (hypercalcemia, mental retardation, elfin face and AS).

- The condition is asymptomatic in most cases and usually discovered during routine examination. However, critical aortic stenosis in infancy leads to cardiomegaly, congestive heart failure and pulmonary edema. Exertional dyspnea or syncope may also occur.
- The ejection systolic murmur is maximally heard over the *aortic area.* It is harsh, rough and loud (grade III to V). It usually propagates to the neck and second aortic area and it is commonly associated with a palpable thrill. In valvular lesion, an aortic ejection click usually precedes the murmur.
- The aortic component of the second sound is weak in severe cases.
- Variable degrees of left ventricular hypertrophy are usually present.
- Chest x-ray reveals poststenotic dilatation of ascending aorta (in valvular lesions) and variable LVH. ECG reveals LVH and echocardiography is diagnostic.

4. Other causes: Several other conditions are associated with ejection systolic murmurs over the pulmonary area and should not be confused with atrial septal defect and pulmonary stenosis. These conditions are:

*a) **Innocent pulmonary ejection murmur:*** It is a soft murmur that changes in intensity with changes in position. It is not associated with any cardiac dysfunction.

*b) **Hemic murmur:*** It is a soft murmur that appears with severe anemia. Intense pallor is evident clinically.

*c) **Pulmonary hypertension:*** In addition to the ejection systolic murmur, dullness, palpable second sound and visible pulsations over the pulmonary area are present. The condition may be primary or secondary to other cardiac diseases. Doppler echocardiography is diagnostic.

*d) **Partial anomalous pulmonary venous return (PAPVR)*** should be also considered. Diagnosis is made by Doppler echocardiography.

*e) **Hypertrophic cardiomyopathy:*** The ejection systolic murmur is heard over the left sternal border and the apex. Echocardiography shows the characteristic asymmetric septal hypertrophy and the subaortic stenosis (see cardiomyopathy).

(b) Pansystolic murmurs

1. Ventricular septal defect (VSD): It is the most common congenital heart disease (25% of all). Patients are, frequently asymptomatic and the condition is accidentally discovered on routine cardiac examination. Moderate and large sized VSD can lead to cardiomegaly and congestive heart failure in infancy. About 60% of cases close spontaneously within 2 - 4 years.

- The pansystolic murmur is mainly heard over the *3rd and 4th left parasternal spaces.* It is a harsh and loud murmur (grade III to V) and it is commonly associated with a palpable thrill.

- The second sound over the pulmonary area is usually loud.
- Biventricular hypertrophy usually occurs with big defects. Cardiomegaly and precordial bulge occurs in infants with big defects.
- Chest x-ray reveals plethoric lung fields and cardiomegaly. In small defects the x-ray is free. ECG is free in small defects or show left or biventricular hypertrophy in large defects. Echocardiography is diagnostic.

2. PDA with pulmonary hypertension: In patent ductus arteriosus with pulmonary hypertension (and in infancy), the diastolic element of the continuous murmur disappears leaving only a pansystolic murmur.

- The pansystolic murmur is mainly heard over the *2nd left parasternal space* (higher than that of VSD).
- The second sound over the pulmonary area is usually loud.
- Variable degrees of left ventricular hypertrophy are usually present.
- Two-dimensional echocardiography and/or Doppler echocardiography can demonstrate the ductus. Color flow mapping can demonstrate the direction of the flow.

3. Mital regurgitation (MR): *Isolated* congenital mitral regurgitation is not common but the condition may *accompany* other cardiac diseases especially endocardial cushion defect and congestive cardiomyopathy. In children above the age of 5 years, *rheumatic* mitral regurgitation should be considered.

- The pansystolic murmur is maximally heard over the *apex* (mitral area). The murmur is usually harsh and loud. It propagates to the axilla.
- The second sound is accentuated in presence of pulmonary hypertension.
- Variable degree of left ventricular hypertrophy is usually present.
- Echocardiography is essential for diagnosis.

4. Tricuspid regurgitation (TR): *Isolated* congenital tricuspid regurgitation is uncommon but the condition may suggest an *Ebstein anomaly* in which cyanosis has not yet developed. *Functional* TR may accompany right sided heart failure.

- The pansystolic murmur is maximally heard over the left or right lower sternal border (lower than that of VSD).
- Hepatomegaly and engorged pulsating neck veins are common.
- Variable degree of RVH is present.
- Echocardiography is essential for diagnosis.

(C) Continuous murmurs

1. Patent ductus arteriosus (PDA): It is a common disease, which accounts for about 10% of all congenital heart diseases. A small patent ductus is usually asymptomatic and only discovered on routine cardiac examination. Large PDA with significant left-to-right shunt is associated with recurrent chest infection, cardiomegaly and congestive heart failure in infancy. The *arterial pulsations are prominent* and can be easily felt due to the wide pulse pressure. The dorsalis pedis pulsations can be easily felt (important).

- The continuous murmur is maximally heard over the *pulmonary area*. The murmur is machinery (with systolic accentuation). It is important to remember that the diastolic element may disappear in early infancy or with pulmonary hypertension leaving only the pansystolic murmur (see pansystolic murmurs).
- The second sound over the pulmonary area is accentuated.
- Variable degree of LVH is usually present.
- Chest x-ray reveals pulmonary plethora, prominent pulmonary artery and variable degree of cardiomegaly. ECG reveals LVH. Two-dimensional echocardiography or Doppler echocardiography can visualize the ductus. Color flow mapping will demonstrate the direction of the flow. Cardiac catheterization and angiography shows the ductal anatomy well.

2. Patent ductus-like diseases: These conditions are characterized by an abnormal arteriovenous communication (not through the ductus) and by findings similar to PDA (i.e. continuous murmur and big pulse pressure). These diseases are:

1. Aorticopulmonary septal defect.
2. Ruptured sinus of Valsalva.
3. Coronary arteriovenous fistula.
4. Aberrant left coronary artery with massive collaterals from the right coronary.

All these conditions are quite rare when compared to PDA and the continuous murmur is usually heard on unusual sites (i.e. not on pulmonary area). Differentiation from patent ductus arteriosus is by two-dimensional echocardiography, Doppler echocardiography or color flow mapping.

3. Truncus arteriosus: In this cyanotic heart disease, the onset of cyanosis is variable and may be delayed to childhood. An ejection systolic murmur or a continuous murmur (without cyanosis) may be the main presentation. Cardiomegaly and congestive heart failure may lead to death in infancy. Echocardiography is essential for diagnosis.

4. Venous hum: It is an *innocent murmur* caused by turbulence of blood in the jugular venous system. It is a soft humming continuous murmur heard over the neck and anterior upper chest. It varies in intensity (increase or decrease) by changing the position of the head. Light compression of the jugular venous system in the neck leads to a decrease or disappearance of the murmur.

- **Continuous murmur with central cyanosis** as with pulmonary atresia and tricuspid atresia are not included here because the main presentation in these conditions is the central cyanosis and not the continuous murmur.

- **Double murmurs** (systolic and diastolic murmurs) should not be confused with the continuous murmurs. An example is VSD and aortic regurgitation (pansystolic and early diastolic murmurs). In children above the age of 5 years, rheumatic double murmurs (as double mitral lesion and double aortic lesions) are commonly present.

2. Disparity in pulsations and Blood pressure

Palpation of superficial pulsations in upper and lower limbs should be a routine essential step in evaluation of the cardiovascular system.

- In upper limbs: Brachial and radial pulsations.
- In lower limbs: Femoral and dorsalis pedis pulsations.

Normally, pulsations are well felt in upper and lower limbs. In conditions with big pulse pressure as PDA, arterial pulsations are prominent and dorsalis pedis pulsations are well felt. On the other hand, in coarctation of the aorta pulsations in lower limbs are weak or absent.

Coarctation of the aorta is a common condition, which accounts for 8% of all congenital heart diseases. It is twice as common in males as it is in females (Turner syndrome should be considered in females). Most cases are asymptomatic and discovered by routine examination. In 10% of cases, cardiomegaly and congestive heart failure occurs in early infancy. The main characteristic features are:

- *Disparity in pulsations between upper and lower limbs.* Pulsations are prominent in upper limbs and weak or absent in lower limbs. An additional simple confirmatory finding is the presence of hot hands and cold feet.
- *Disparity in blood pressure between upper and lower limbs:* Normally blood pressure in lower limbs is higher than that of upper limbs. In case of coarctation, blood pressure increases in upper limbs and decreases in lower limbs (blood pressure in lower limbs is less than that of upper limbs).
- *Ejection systolic murmur* may be heard at the apex, left sternal border or interscapular area. It is caused by the flow across the coarctation or through the collateral vessels. The interscapular murmur is characteristic.
- Chest x-ray and ECG are not useful in diagnosis and are usually normal. Two-dimensional echocardiagraphy and Doppler echocardiography can visualize the segment of coarctation. Cardiac catheterization and aortography may be done when associated anomalies are present.

3. Cardiomegaly and congestive heart failure in infancy

Cardiomegaly and congestive heart failure may be the initial presentation of noncyanotic congenital heart diseases. Manifestations of congestive heart failure may be ***chronic*** and gradually developing or may be ***acute*** when it is associated or precipitated by respiratory infections (see acute and chronic congestive heart failure). The main causes are:

1. Big left-to-right shunt: Big ventricular septal defect is the commonest cause. Large sized patent ductus arteriosus is also a common cause. Low atrial septal defects as ostium primum defect and artioventricular canal (endocardial cushion defect) usually present with cardiomegaly and congestive heart failure (see cardiac murmurs).

2. Severe or critical aortic stenosis: Clinical diagnosis is not difficult. Harsh and loud ejection systolic murmur is heard over the aortic area.

3. Severe coarctation of the aorta: Disparity of pulsations between upper and lower limbs is well evident.

4. Endomyocardial diseases: Several sporadic and inherited conditions are characterized by cardiomegaly and congestive heart failure in infancy. Nonspecific murmurs or pansystolic murmur of mitral regurgitation is a common associated finding. Echocardiography is essential for demonstration of the myocardial disease (poor contractions) and for differentiation from other conditions with a similar presentation. These diseases are:

- ***Endocardial fibroelastosis:*** It is a condition of unknown etiology characterized by fibroelastic thickening of the myocardium of the left ventricle and occasionally of the valves. The illness usually presents in early infancy (below 6 months) with cardiomegaly and severe congestive heart failure. Chest x-ray reveals cardiomegaly and ECG shows left atrial and left ventricular hypertrophy. Echocardiography demonstrates the thickened endocardium and the poorly contracting left ventricle.
- ***Congestive (dilated) cardiomyopathy:*** It is an idiopathic condition characterized by massive dilatation of the ventricles especially the left. The disease can occur at any age including infancy. The manifestations of congestive heart failure are usually insidious in onset and chronic but acute failure may also occur. Chest x-ray reveals cardiomegaly and ECG shows atrial enlargement and left ventricular hypertrophy. Echocardiography demonstrates the dilated ventricles (especially the left) and the poor myocardial contractions.
- ***Aberrant left coronary artery from the pulmonary artery:*** This anomaly usually presents in early infancy with moderate to massive cardiomegaly and congestive heart failure. Chest x-ray reveals cardiomegaly and ECG shows changes similar to anterior or lateral myocardial infarction. Two-dimensional echocardiography is not reliable for diagnosis. Aortography is diagnostic and shows immediate opacification of the right coronary artery only.
- ***Inherited metabolic diseases:*** Metabolic cardiomyopathy in infancy may occur with several inherited metabolic diseases but all are rare
  - *Glycogenosis type II (Pompe disease):* It presents in neonatal period with severe hypotonia, protruded tongue and cardiomyopathy (see floppy infant).
  - *Carnitine deficiency:* It is a disorder of intermediary carbohydrate metabolism characterized by recurrent episodes of lactic acidosis and cardiomyopathy.
  - *Mucolipidois type II (I-cell disease):* It presents in neonatal period with coarse features, hypertrophied gums and other Hurler-like features (see metabolic diseases and Hurler-like disorders).
  - *Generalized gangliosidosis (GM1 type 1):* It presents with Hurler-like manifestations ([illegible]).

2. Acute Rheumatic Fever

Modified John's criteria for diagnosis of rheumatic fever

Major manifestations	Minor manifestations	Evidence of recent streptococcal infection
Polyarthritis Carditis Chorea Erythema marginatum Subcutaneous nodules	Fever Arthralgia Previous rheumatic fever Acute phase reactants Leukocytosis Raised ESR, CRP Prolonged P-R interval (ECG)	Recent scarlet fever Positive throat culture Antistreptococcal antibodies Antistreptolysin O (ASO) Antistreptokinase Antihyaluronidase

Rheumatic fever is an ***autoimmune disease*** following upper respiratory tract infection with group A beta hemolytic streptococci. A *latent period* of 1-3 weeks between throat infection and onset of rheumatic fever is always present. Although rheumatic fever can occur at any age except infancy, most cases occur between *5-15 years* when streptococcal infections are most frequent. It is important to remember that there is no *single* clinical or laboratory finding which is pathognomonic for rheumatic fever and the diagnosis is usually based on a *combination* of manifestations characteristic of this disease and with exclusion of other diseases which may mimic it.

Modified John's criteria are generally accepted for guidance in the diagnosis of rheumatic fever (see above). Diagnosis of rheumatic fever depends on 3 criteria:

1. Two major manifestations or one major and two minor manifestations.
2. Evidence of recent streptococcal infection.
3. Exclusion of other diseases, which may mimic rheumatic fever.

Exceptions to the above rules are:

1. Chorea: As rheumatic chorea can be the only manifestation of rheumatic fever, diagnosis can be made in absence of any other major or minor manifestations provided other causes of chorea have been excluded.

2. Insidious or late onset carditis: Diagnosis of rheumatic carditis can be made in absence of any other major or minor manifestation or preceding streptococcal infection provided other causes of carditis have been excluded.

3. Rheumatic recurrence (rheumatic activity): In patients with documented chronic rheumatic heart disease, the diagnosis of rheumatic recurrence can be made in absence of major manifestations. Minor manifestations (fever, arthralgia or acute phase reactants) and recent evidence of streptococcal infection are enough to make the diagnosis.

Important remarks

1. Diagnosis based on 2 major manifestations is stronger than that based on one major and 2 minor manifestations.
2. Arthralgia should not be considered as a minor manifestation in patients with polyarthritis.
3. Prolonged P-R interval should not be also considered as a minor manifestation in patients with carditis.
4. High fever above 39.5°C or 40.0°C is very unusual in rheumatic fever and careful re-evaluation for other possibilities is important.
5. Previous history of rheumatic fever should not be accepted as a minor manifestation without careful analysis of the history and documented evidence of the previous streptococcal infection (i.e. reliable history and previous investigations).
6. In patients presenting with fever and arthralgia, presence of high sedimentation rate and high ASO (above 400 Todd units) are *not* enough to make the diagnosis because of absence of major manifestations.
7. Leukocytosis, raised ESR and raised CRP are all considered as one minor manifestation (acute phase reactants).
8. Arthritis which is not polyarticular or not migratory should never be accepted as a rheumatic arthritis. Monoarticular arthritis or chronic arthritis can never be rheumatic.
9. Exclusion of other diseases, which may simulate rheumatic fever, is very important. *Acute leukemia* should be always in mind in patients presenting with fever and arthritis. *Systemic lupus* should be also considered because both arthritis and carditis are common. *Cardiac infections* (endocarditis, myocarditis or pericarditis) should be also in mind in patients presenting with carditis.
10. Overdiagnosis of rheumatic fever should be avoided since it may result in long-term unnecessary antimicrobial prophylaxis and serious psychological effects. Furthermore, such a diagnosis will mislead other physicians who may consider the previous diagnosis as a minor manifestation.

Diagnosis of major manifestations

1. Polyarthritis: It is the most common manifestation, occurring in 75% of cases during the acute stage. It is characteristically *polyarticular* (affecting many joints) and involving mainly the *large joints* (as knees, ankles, elbows and wrists). It is also *transient* (less than one week in the affected joint) and *migratory* (leaves the joint without destruction to affect other joints). The inflamed joint is usually swollen, red, hot, and very tender with marked limitation of movements. It also characteristically shows *dramatic response* to anti-inflammatory drugs where arthritis may disappear in 24 hours. It is important again to remember that the diagnosis of rheumatic arthritis should never be made in monoarticular, non-migratory or chronic arthritis.

2. Carditis: It is the most serious manifestation as it may be fatal or may lead to permanent valvular damage (chronic rheumatic heart disease). It occurs in about 50%of cases. It may be *mild or severe* and without therapy it remains for a period ranging from 6 weeks to 6 months. Occasionally it is insidious and appears after several weeks of onset *(late-onset carditis)* and in other occasions it may be asymptomatic *(silent carditis)* and discovered later (after years) with the picture of chronic rheumatic heart disease. Carditis of rheumatic fever is a *pancarditis* involving endocardium, myocardium and pericardium. Diagnosis of carditis depends on the following criteria:

• ***Myocarditis:*** Disproportionate tachycardia (to age and fever) and muffled heart sounds are the most important manifestations. Gallop rhythm may be evident. Prolonged P-R interval on an ECG confirms the diagnosis.

• ***Endocarditis:*** Mitral valve is the most frequently involved valve but both mitral and aortic valves may be affected. Mitral valvulitis leads to mitral regurgitation (significant apical systolic murmur) and aortic valvulitis leads to aortic regurgitation (early diastolic left parasternal murmur). Stenotic valvular lesions do not occur except in chronic rheumatic heart disease.

• ***Pericarditis:*** Friction pericardial rub may be heard over the precordium and pericardial effusion may occur but usually not significant and only detected by echocardiography.

•***Complications:*** Congestive heart failure of variable severity is common and arrhythmias may be also evident. Cardiomegaly usually occurs with significant carditis and with congestive heart failure.

3. Chorea: It occurs in 10% of cases and usually appears after several weeks or even several months of onset. Clinical diagnosis depends on the presence of choreic movements, emotional lability, hypotonia and several typical signs:

(i) Darting tongue: The tongue cannot be protruded for a longer than a few seconds.
(ii) Choreic hand: The extended hands show wrist flexion and fingers extension.
(iii) Pronator sign: The arm and palm turn out when held above the head.
(iv) Milk maid's grip: With shaking hands, relaxing and tightening handshake occurs.

• Associated rheumatic heart disease is present in one third of cases.
• It usually subsides spontaneously over several weeks or few months. Recurrences are common (see also movement disorders).

4. Erythema marginatum: It occurs in only 5% of cases and mainly in patients with chronic rheumatic heart disease. It forms wavy lines or rings of sharp margins mainly over the trunk. (serpiginous-looking lesion). The rash can be mistaken with the rash of Lyme disease (see arthritis).

5. Subcutaneous nodules: It occurs in only 1% of cases and mainly in patients with severe carditis. They appear as rounded pea-sized, firm and painless nodules over bony prominences as elbows and knees and over the spine.

3. Chronic Rheumatic Heart Disease

Permanent valvular damage	Complications
Mitral valve (commonest) Aortic valve (common) Tricuspid valve (rare) Pulmonary valve (very rare) (Regurgitation is commoner)	Cardiomegaly Congestive heart failure Pulmohary hypertension Rheumatic activity Infective endocarditis Cardiac arrhythmias

Chronic rheumatic heart disease results from the permanent valvular damage, which occurs due to severe initial attack or recurrent attacks of rheumatic carditis. Occasionally, history of previous illness suggesting rheumatic fever is completely absent (asymptomatic or silent carditis).

- Why rheumatic?
- What are the valvular lesions?
- What are the complications?

1. Why rheumatic?

Criteria suggesting rheumatic origin are:

1. Age of onset above 5 years (or at least above 3 years).
2. History of recurrent attacks of tonsillitis.
3. Reliable history of previous rheumatic fever (including previous investigations).
4. Nature of the valvular lesion. The predilection to mital and aortic valves and the multiplicity of valvular lesions are characteristic of rheumatic heart disease.

2. What are the valvular lesions?

Recognition of the valvular lesions depends on the characteristic murmurs.

1. Mitral valve is the most commonly affected valve. Isolated regurgitation is commoner than isolated stenosis but double mitral lesion is common.

a) ***With mitral regurgitation***, an apical harsh pansystolic murmur is present which is commonly associated with a palpable thrill. It usually propagates to the axilla. Variable degree of left ventricular hypertrophy is usually present.

b) ***With mitral stenosis***, an apical mid-diastolic rumbling murmur is present with variable degrees of right ventricular hypertrophy. With longstanding lesions, pulmonary hypertension occurs (see below).

c) ***With double mitral lesion***, both murmurs are heard and biventricular hypertrophy may be present.

2. Aortic valve is the next commonly involved valve. Both mitral and aortic involvement is commoner than isolated aortic involvement. Aortic regurgitation is commoner than aortic stenosis but double aortic lesion may occur.

a) With aortic regurgitation, a soft blowing early diastolic murmur is heard over the left third parasternal area and may propagate to aortic area and apex. Left ventricular hypertrophy is present in severe cases. *Peripheral signs* resulting from reflux of blood through aortic valve are present. These signs of big pulse pressure include: bounding peripheral pulsations, water hummer pulse, pistol shot (auscultated over big arteries) and elevated systolic and lowered diastolic blood pressure.

b) With aortic stenosis, harsh ejection systolic murmur over the aortic area is evident and usually propagates to the neck. Associated systolic thrill and left ventricular hypertrophy are present in severe cases. It is important to emphasize that isolated aortic stenosis as a sole cardiac lesion is almost always congenital and not rheumatic.

c) With double aortic lesions, both murmurs are heard and left ventricular hypertrophy occurs.

3. Tricuspid valve lesions are rare. However, functional tricuspid regurgitation may occur with severe right ventricular dilatation secondary to severe mitral lesions. A pansystolic murmur is heard over the left lower sternal border, which characteristically increases in intensity during inspiration. Visible jugular pulsations and hepatomegaly are usually present.

3. What are the complications?

Several complications can occur especially in severe cases and should be thoroughly excluded in every case. These complications include cardiomegaly, congestive heart failure, pulmonary hypertension, rheumatic activity, infective endocarditis and cardiac arrhythmias.

1. Cardiomegaly: Assessment of the cardiac size, both clinically and radiologically, is extremely important from the prognostic point of view and for decision regarding the necessity for surgery. Variable degrees of cardiomegaly usually occur and depend on the number of valvular lesions, severity of lesions and duration of illness. Several years may elapse before a significant cardiomegaly becomes evident.

a) Mild cardiomegaly is difficult to detect clinically. Radiological and echocardiographic studies are essential to exclude cardiomegaly.

b) Moderate cardiomegaly can be detected clinically with inspection and palpation. With *right ventricular hypertrophy,* the apex is shifted outwards and the maximal impulse is felt in the left parasternal area. Visible left parasternal and epigastric pulsations are present. With *left ventricular hypertrophy,* the apex is shifted downwards and outwards and the maximal impulse is felt over the apex.

c) Huge long standing cardiomegaly is associated with well evident precordial pulge and manifestations of ventricular enlargement become more pronounced.

2. Congestive heart failure (CHF): It is usually chronic and appearing insidiously but episodes of acute failure are also common and usually precipitated by: (1) rheumatic activity, (2) infective endocarditis and (3) severe chest infection.

(a) ***Chronic CHF:*** The manifestations depend on the severity of the valvular lesions and the duration of illness. History is extremely important.

- *In mild cases*, exertional dyspnea (dyspnea following mild exertion) is the main manifestation. Detailed and unhurried history is very essential and is frequently the decisive criterion regarding the necessity of surgery.
- *In moderate cases*, dyspnea on mild exertion and signs of systemic congestion appear (engorged neck veins, enlarged tender liver and oedema of lower limbs).
- *In severe cases*, dyspnea at rest is present and manifestations of systemic congestion become more evident. Ascites and hydrothorax may be present.

(b) ***Acute CHF:*** The manifestations depend on the degree of cardiac dysfunction and the severity of the precipitating factors (see above).

- *In mild cases*, the cardinal clinical triad is present (disproportionate tachycardia, disproportionate tachypnea and enlarged tender liver).
- *In moderate cases*, manifestations of marked pulmonary congestion appear (respiratory distress with evident intercostal and subcostal retractions and fine basal crepitations). In more advanced cases, pulmonary edema occurs (serve respiratory distress and coarse bubbling crepitations). Chest x-ray reveals a hazy to opaque infiltrate (see Basic Pediatric Radiology).
- *In severe cases*, the heart becomes unable to pump the blood effectively into the circulation and cardiogenic shock occurs (severe hypotension and poor peripheral perfusion).

3. Pulmonary hypertension: With severe longstanding mitral lesion, especially mitral stenosis, chronic pulmonary venous hypertension occurs and eventually results in pulmonary arterial hypertension.

- Symptoms of pulmonary hypertension mainly include exertional dyspnea, fatigability and occasionally syncopal attacks. Other causes of exertional dyspnea especially chronic congestive heart failure and chronic pericardial disease should be considered.
- Cardiac signs are initially limited to a soft ejection systolic murmur over the pulmonary area. With progression, dullness, loud and palpable second sound (diastolic shock) and visible pulsations over the pulmonary area appear.
- Chest x-ray reveals dense hilar shadow, prominent pulmonary segment and right ventricular enlargement. ECG confirms the right ventricular hypertrophy. Doppler echocardiography and pulmonary artery catheterization are the diagnostic procedures.
- It is important to remember that ***chronic*** pulmonary hypertension can follow several other conditions and it may be also idiopathic and progressive (primary pulmonary hypertension). It is also important to realize that pulmonary hypertension can be ***acute*** and transient as in severe septicemia, severe metabolic acidosis and shock lung.

Causes of chronic pulmonary hypertension

Hyperkinetic pulmonary hypertension (lung plethora)
With large left-to-right shunt (as VSD, PDA, ostimum primum defect).

Venous pulmonary hypertension (lung congestion)
Mitral stenosis, chronic left heart failure.

Arterial pulmonary hypertension
Persistent pulmonary hypertension of the newborn.
Primary pulmonary hypertension (rare fatal disease).
Secondary to long standing "hyperkinetic" and "venous" hypertension.
Secondary to chronic airway obstruction or chronic lung disease (cor pulmonale).

4. Rheumatic activity (recurrence): Rheumatic fever, particularly carditis, is frequently recurrent. Diagnosis of relapses (rheumatic activity) in a chronic rheumatic heart disease is considered in any of the following 4 situations: (1) recent fever and arthritis or arthralgia, (2) change in the character of the previously known murmurs or appearance of new murmurs, (3) an episode of myocarditis or congestive heart failure and (4) presence of pericardial involvement (friction rub or pericardial effusion). In these situations, laboratory confirmation is essential especially an evidence of recent streptococcal infection (raised ASO titer above 400 Todd units).

5. Infective endocarditis: This serious complication should be considered in the presence of any of the following4 situations: (1) unexplained prolonged low grade fever, (2) change in the character of previously known murmurs or appearance of new murmurs, (3) an episode of acute congestive heart failure and (4) Neurological embolic manifestations as cranial nerve palsies or hemiplegia. Blindness is a catastrophic embolic manifestation. In these situations, urgent blood cultures and immediate management are essential.

6. Cardiac arrhythmias: Several arrhythmias may occur with severe lesions or iatrogenically due to digitalis toxicity. The main arrhythmias are:

- ***Atrial fibrillation:*** The cardiac rhythm is very irregular (you can not count 4 successive regular beats). Two successive long pauses are common.
- ***Extrasystole:*** The cardiac rhythm is regularly irregular (each premature beat is followed by a compensatory pause).
- ***Heart block:*** It is suspected with bradycardia (heart below 60/minute). Variable degrees may occur (first, second or third degree) and can be demonstrated by ECG. Digitalis toxicity is the main cause.
- ***Supraventricular or ventricular tachycardia*** is usually caused by digitalis toxicity. ECG is essential for diagnosis.

In every case of chronic rheumatic heart disease accurate history of drug therapy especially digoxin is very important. Dosage of digoxin should be checked because both underdosage and overdosage are commonly encountered. This is particularly important in case of arrhythmia or when manifestations of failure are not properly controlled.

Relevant investigations in chronic rheumatic heart disease

Chest and heart x-ray

Assessment of cardiac size (normal or enlarged).
Pulmonary segment (normal or large).
Lung fields (normal, lung congestion or pulmonary edema).

Electrocardiogram (ECG)

Ventricular hypertrophy (right, left or both).
Diagnosis of arrhythmias.

Echocardiography

Detection of valvular lesions.
Detection of vegetations in infective endocarditis.
Evaluation of cardiac size and function.

Investigations to prove rheumatic activity

Acute phase reactants (ESR, CRP, CBC).
Evidence of recent streptococcal infection (ASO titer, throat culture).

Repeated blood cultures

With suspected bacterial endocarditis.

Serum digoxin level

With suspected digitalis toxicity.
(Therapeutic digoxin level in children is 1 - 2 ng/ml).

4. Cardiac Infections

Endocarditis	Myocarditis	Pericarditis
Infective endocarditis	**Infective myocarditis**	**Infective pericarditis**
Bacterial	Bacterial (toxic)	Bacterial (purulent)
Viral	Viral	Viral (benign)
Other organisms	Other organisms	Others (tuberculous)
Noninfective endocarditis	**Noninfective myocarditis**	**Noninfective pericarditis**
Rheumatic Fever	Rheumatic Fever	Rheumatic Fever
Systemic lupus (SLE)	Systemic lupus (SLE)	Systemic lupus (SLE)
	Rheumatoid arthritis	Rheumatoid arthritis
	Metabolic	Metabolic (uremia)
	Drugs, radiotherapy	Drugs, radiotherapy

Infections of the heart are serious life-threatening diseases, which may be acute or chronic, affecting one or more components and occurring in normal heart or on top of a pre-existing cardiac disease.

The causative organisms differ according to the site of infection. Infective endocarditis is mostly bacterial in origin while infective myocarditis and infective pericarditis can be bacterial or viral. Moreover, coxsackievirus B is the principal viral agent in both conditions and this explains why myocarditis and pericarditis commonly coexist. The onset and course of illness are related to the causative organism. Bacterial infections are more acute and more serious than viral infections.

1. Infective endocarditis: It is a serious potentially fatal infection, which principally occurs in children with pre-existing congenital or rheumatic heart disease. However, the disease can also occur in children with a normal heart. A predisposing factor (as surgery, dental procedure or intravenous catheter) is present in one third of cases.

• Two organisms account for the majority of cases; streptococcus viridans (50%) and staphylococcus aureus (30%). Other bacteria as pseudomonas, hemophilus influenza and streptococcus pneumonia may be occasionally responsible. Viruses or fungi (candida) are rare causative agents.

• The onset of illness can be acute (staphylococcal) or more commonly subacute or insidious (streptococcal).

• Clinical manifestations can be divided into 3 groups, which may be present separately or in different combinations. Presence of any of these manifestations in a patient with pre-existing cardiac disease is an indication for immediate diagnostic measures and management.

Clinical presentations of infective endocarditis

Nonspecific manifestations
Unexplained prolonged low grade or moderate fever.
Fatigue, anorexia and weight loss. Myalgia, arthralgia and headache.
Splenomegaly is common.

Cardiac manifestations
Change in the character of pre-existing murmurs.
Appearance of new murmurs.
Congestive heart failure (due to toxic myocarditis or vegetations on valves).

Embolic manifestations
Focal neurological signs as cranial nerve palsies or hemiplegia.
Glomerulonephritis (hematuria, red cell casts).
Blindness is a catastrophic complication.

Diagnostic procedures include repeated blood culture (for detection of causative organism) and echocardiography (for detection and localization of the vegetations). Other nonspecific laboratory investigations as CBC, CRP and ESR are useful for follow-up and evaluation of therapy.

2. Infective myocarditis: It is a serious infection, which may be acute or chronic, bacterial or viral and benign or fatal. Chronic viral myocarditis may lead to congestive (dilated) cardiomyopathy.

- The main causative organisms are bacteria and viruses. Bacterial myocarditis is mainly toxic and it occurs with diphtheria, typhoid, pneumonia and septicemia. Viral myocarditis is mainly caused by coxsackievirus B which may also involve the pericardium (myopericarditis). Other viruses as mumps, herpes and influenza viruses may be occasionally responsible.
- The onset can be acute (bacterial or viral) or insidious (chronic viral). In acute bacterial myocarditis, the precipitating bacterial infection (as pneumonia or septicemia) are the dominating features while in viral myocarditis the cardiac manifestations are the only evident features.
- Clinical manifestations can be divided as acute and chronic.

Clinical presentations of infective myocarditis

Acute myocarditis
Disproportionate tachycardia, muffled heart sounds, gallop rhythm, cardiomegaly.
Acute congestive heart failure (may lead to cardiogenic shock).
Arrhythmias (may be fatal).

Chronic myocarditis
Gradually progressive chronic congestive heart failure.
Arrhythmias.
Congestive (dilated) cardiomyopathy.

• Chest x-ray reveals cardiomegaly and may be pulmonary edema. ECG shows sinus tachycardia, reduced QRS complex voltage and abnormal ST segment and T wave. Echocardiography demonstrates the poor ventricular function and possibility mitral regurgitation or associated pericardial effusion. ESR and cardiac enzymes (CPK, LHD) may be elevated. In prolonged or chronic cases, percutaneous endomyocardial biopsy is diagnostic and can differentiate the condition from other causes of cardiomyopathy especially carnitine deficiency, mitochondrial defects and storage diseases.

• Myocarditis should not be confused with others causes of cardiomegaly without heart murmurs. Echocardiography, Doppler echocardiography and occasionally endomyocardial biopsy are needed for differentiation.

Causes of cardiomegaly without heart murmurs

Endomyocardial disease
- Myocarditis (viral or idiopathic).
- *Endocardial fibroelastosis.*
- *Glycogen storage disease type II (Pompe disease).*

Coronary artery disease causing myocardial insufficiency
- Aberrant origin of left coronary from the pulmonary artery.
- Collagen disease (polyarteritis nodosa).
- Kawasaki disease (mucocutaneous lymph node syndrome).

Congenital heart disease
- Coarctation of the aorta in infants.
- Ebstein anomaly.

Other cardiac causes
- Pericardial effusion (large cardiac shadow on chest x.ray).
- Cardiac tumours (Rhabdomyoma, fibroma, myxoma, sarcoma).
- Paroxysmal atrial tachycardia with congestive heart failure.

Extracardiac causes
- Cor pulmonale (chronic upper airway obstruction or chronic lung disease).
- Protein calorie malnutrition and infantile beriberi.
- Severe anemia.

3. Infective pericarditis: It is a serious infection, which may be acute or chronic and benign or fatal. The onset, course of illness and prognosis are largely dependant on the causative organism:

a) Viral (acute benign) pericarditis is principally caused by coxsackievirus B, other viruses as Ebstein-Barr virus; adenovirus and influenza virus may be responsible. The onset is acute with mild fever and chest pain. The illness is mild, the course is benign and recovery over weeks is the rule.

b) ***Bacterial (purulent) pericarditis*** is caused by staphylococci, streptococci, pneumococci, meningococci, tularemia or hemophilus influenza. The illness usually follows other bacterial infections as pneumonia, epiglottitis or osteomyelitis. The onset is acute with high fever, chest pain, dyspnea and cough. The illness is severe, the course is fulminant and acute cardiac tamponade (compression) occurs and may be fatal. In survivors constrictive pericarditis may occur after months or years.

c) ***Tuberculous pericarditis*** occurs secondary to rupture of a mediastinal lymph node into a pericardial space or due to hematogenous spread. The onset is often insidious and the condition usually presents with the picture of constrictive pericarditis (small heart, hepatomegaly and ascites).

Clinical manifestations of acute bacterial (purulent) pericarditis

- High fever, dyspnea and cough.
- Precordial pain: Sharp and stabbing, increases by lying and decreases by sitting.
- Pericardial friction rub: May be heard over the precordium.
- Acute cardiac tamponade (with considerable pericardial effusion)
  - Tachycardia with distant muffled heart sounds.
  - Enlarged heart with quiet precordium (dullness outside the apex).
  - Systemic congestion (distended neck veins, hepatomegaly).
  - Pulsus paradoxus (inspiratory lowering of blood pressure greater than 20 mm Hg).

Pulsus paradoxus is an exaggeration of the normal reduction of systolic blood pressure during inspiration. Normally, inspiratory lowering of 5mm Hg is observed. Value between 10 -20 is equivoral and value above 20 mm Hg is diagnostic.

Causes of pulsus paradoxus are:

1. Pericardial disease (effusion, constrictive pericarditis).
2. Endocardial disease affecting compliance (endocardial fibroelastosis).
3. Lung disease (acute asthma, pneumonia).

- Once the diagnosis of acute pericarditis is clinically suspected, *echocardiography* is reliable for diagnosis and for evaluation of the size and progress of the pericardial effusion. With considerable effusion, *pericardiocentesis* (closed pericardial aspiration) is indicated in symptomatic relief and for culture and sensitivity studies. Chest x-ray cannot easily differentiate between cardiomegaly and pericardial effusion except in severe cases (see Basic Pediatric Radiology).

- Clinical differentiation between acute myocarditis and acute pericarditis can be difficult because in both conditions tachycardia, muffled heart sounds, engorged neck veins and hepatomegaly are present. Moreover, both conditions commonly coexist (myopericarditis). Echocardiography is essential for differentiation.

- Clinical differentiation between constrictive pericarditis and chronic liver disease can be difficult because in both conditions hepatomegaly and ascites are the main presentation. Echocardiography should be a routine in unexplained hepatomegaly with ascites.

5. Cardiomyopathy

Primary cardiomyopathy	Secondary cardiomyopathy
Hypertrophic cardiomyopathy	Genetic (familial) cardiomyopathy
Dilated (congestive) cardiomyopathy	Collagen (rheumatic) cardiomyopathy
Restrictive cardiomyopathy	Toxic (drug induced) cardiomyopathy
	Nutritional and endocrinal cardiomyopathy

Cardiomyopathy is a chronic myocardial disease characterized by poor myocardial function, which is not related to a congenital heart disease, acquired valvular disease or coronary artery disease.

A) PRIMARY CARDIOMYOPATHY

In this group, involvement of the cardiac muscle is the only manifestation.

1. Hypertrophic cardiomyopathy: It is characterized by massive ventricular hypertropby, mainly the left ventricle, and asymmetric hypertrophy of the septum. The condition is also known as idiopathic hypertrophic subaortic stenosis and asymmetric septal hypertrophy. An autosomal dominant inheritance is observed in some families.

- The disease can occur at any age including infants. Most children are asymptomatic but exertional dyspnea, fatigue, chest pain or syncope may occur.
- Cardiac examination reveals an ejection systolic murmur maximally heard over the left sternal border and the apex. Left ventricular hypertrophy is evident. Clinical differentiation from valvular aortic stenosis depends on the absence of ejection click and normal second sound.
- Chest x-ray reveals mild cardiomegaly and ECG shows left ventricular hypertrophy. Echocardiography is diagnostic and it reveals the characteristic asymmetric ventricular septal hypertrophy.
- The prognosis is unpredictable as sudden death may occur.

2. Dilated (congestive) cardiomyopathy: It is characterized by massive ventricular dilatation, mainly the left ventricle, and huge cardiomegaly. The cause is unknown in most cases but familial conditions (carnitine deficiency, mitochondrial disease) or viral origin (following viral myocarditis) may be responsible.

- The disease can occur at any age including infants. Most cases present with gradual progressive chronic congestive heart failure.
- Cardiac examination reveals cardiomegaly and pansystolic murmurs of mitral and tricuspid regurgitation.
- Chest x-ray reveals cardiomegaly and pulmonary congestion and ECG shows atrial enlargement and left ventricular hypertrophy. Echocardiography demonstrates the

characteristic massive dilatation of ventricles and the poor myocardial contractions. Myocardial biopsy may be needed to exclude familial conditions.

- The course is gradually progressive. Remissions and relapses may occur.

3. Restrictive cardiomyopathy: It is characterized by poor ventricular compliance with inadequate ventricular filling during diastole. The illness may occur with hypereosinophilic syndromes (as Loffler syndrome and eosinophilic myocarditis).

- The illness presents clinically with a picture similar to that of constrictive pericarditis (dyspnea, distended neck veins, hepatomegaly and may be ascites).
- Chest x-ray shows mild to moderate cardiomegaly and ECG shows prominent P wave. Echocardiography is diagnostic and it demonstrates the characteristic poor ventricular filling and excludes constrictive pericarditis.
- Prognosis is generally poor.

Primary cardiomyopathies (Murmurs and differential diagnosis)

Disease	Murmur	Differential diagnosis
Hypertrophic cardiomyopathy	Ejection systolic	Aortic stenosis
Dilated (congestive) cardiomyopathy	Pansystolic	CHF
Restrictive cardiomyopathy	No murmurs	Constrictive pericarditis

B) SECONDARY CARDIOMYOPATHY

In this group, involvement of the cardiac muscle is *not the only manifestation* but is occurs secondary to a systemic illness.

1. Genetic (familial) cardiomyopathy: The main causes are glycogenosis type II (Pompe disease), mucopolysaccharidosis, Hurler-like disorders and Duchenne muscular dystrophy.

2. Collagen (rheumatic) cardiomyopathy: The main causes are systemic lupus erythematosus, rheumatoid arthritis and dermatomyositis.

3. Toxic (drug induced) cardiomyopathy: Iron overload (hemosiderosis), cancer chemotherapy (especially adriamycin) and radiotherapy are the main causes.

4. Nutritional and endocrinal cardiomyopathy: Thiamine deficiency (Beriberi) and protein deficiency (kwashiorkor) are the main nutritional cases while infant of diabetic mother; hypothyroidism and hyperthyroidism are the main endocrinal causes.

6. Congestive Heart Failure

Acute congestive heart failure	Chronic congestive heart failure
Cardiac causes	**Congenital heart disease (CHD)**
Acute myocarditis (Infective, rheumatic)	Cyanotic CHD
Infective endocarditis	Noncyanotic CHD
Myocardial ischemia (Shock, hypoxia)	**Acquired heart disease**
Acute arrhythmias	Rheumatic heart disease
Extracardiac causes	Systemic lupus erythematosus
Acute hypervolemia (preload failure)	**Cardiomyopathy**
Acute hypertension (afterload failure)	Primary cardiomyopathy
Acute-on-chronic	Secondary cardiomyopathy
With exacerbations	**Cor pulmonale**
With infections	Chronic airway obstruction
	Chronic lung disease

Heart failure is the inability of the heart to pump blood in an amount sufficient to the body requirements. According to the mechanism of dysfunction heart failure can result from the following:

1. Contractility failure: It results from *poor myocardial contraction* as in myocarditis, myocardial ischemia and cardiomyopathy.

2. Preload failure: It results from *volume load* on the right side of the heart as in hypervolemia (acute renal failure, anemia, excessive I.V. fluids) or big left to right shunt (ASD, VSD, PDA).

3. Afterload failure: It results from *pressure load* on the left side of the heart as in hypertension or left side obstruction (Coarctation, AS).

4. Arrhythmic failure is due to *extreme changes in heart rate* that decrease the cardiac output as in extreme tachycardia (low stroke volume) or extreme bradycardia (slow heart rate).

According to the pathophysiological changes, clinical manifestations of congestive heart failure can be grouped into 3 categories:

(i) Signs of impaired myocardial contraction as tachycardia, cardiomegaly, gallop rhythm, cold extremities, sweating and may be cardiogenic shock.

(ii) Signs of pulmonary congestion as tachypnea, retractions, wheezing, crepitations and may be pulmonary edema.

(iii) Signs of systemic venous congestion as hepatomegaly, neck vein distention and edema.

A) ACUTE CONGESTIVE HEART FAILURE

In acute congestive heart failure, manifestations of cardiac dysfunction appear acutely and are *well evident at rest*. Clinical diagnosis depends on the presence of the clinical triad of tachycardia, tachypnea and enlarged tender liver. Cardiomegaly is usually present but may be difficult to elicit clinically.

Clinical assessment of the severity is important for the proper choice of the line of therapy and for monitoring the course of illness. In mild cases, only the manifestations of acute failure are evident. In moderate cases, marked pulmonary congestion occurs and leads to pulmonary edema and respiratory failure. In severe cases, marked reduction of cardiac output occurs and leads to cardiogenic shock.

Clinical grading of acute congestive heart failure

Grade I: Heart failure only

Disproportionate tachycardia (disproportionate to age and temperature).
Disproportionate tachypnea (disproportionate to age and temperature).
Hepatomegaly (congested tender liver).
Cardiomegaly (well evident radiologically).

Grade II: Heart failure and respiratory failure (Pulmonary edema)

Moderate to severe respiratory distress (retractions, ± cyanosis)
Expiratory wheezing, fine basal or coarse bubbling crepitations.

- Chest x-ray: Marked pulmonary congestion or pulmonary edema.
- Arterial blood gases: Low PaO_2 (below 50 mm Hg), ± high $PaCO_2$.

Grade III: Heart failure and circulatory failure (cardiogenic shock)

Peripheral hypoperfusion (mottled skin, cold extremities).
Hypotension (measurement of blood pressure is essential).
Vital organ hypoperfusion (kidneys, lungs, GIT, brain, heart).

- Doppler echocardiography: Reduced cardiac output.
- Pulmonary artery catheterization: Accurate measurement of cardiac output.

- Heart rate and respiratory rate should be counted over 1 minute in a quiet patient.
- Measurement of blood pressure is essential for detection of hypertension or shock.
- Distended neck veins, edema, gallop rhythm are variable findings and may be absent.
- Chest x-ray is useful for detection of cardiomegaly and pulmonary edema.
- ECG is useful for detection of arrhythmias and myocarditis.
- Echocardiography is useful for detection of poor contraction and endocarditis.
- Doppler echocardiography is useful for detection of low cardiac output.
- Arterial blood gases are essential for detection of respiratory failure.
- Pulmonary artery catheterization may be needed in cardiogenic shock.
- Evaluation of renal function is important because renal failure may be the cause of heart failure and, on the other hand, cardiogenic shock leads to renal failure.

Diagnosis of the cause of acute failure requires consideration of the age, associated clinical findings and some investigations.

- At any age, myocarditis, arrhythmias and acute renal failure can occur.
- In infants, coronary artery disease (Kawasaki disease) or anomalies (aberrant origin of left coronary from pulmonary artery) should be remembered.
- In children, rheumatic fever and glomerulonephritis should be considered.
- It should be also remembered that acute failure could occur on top of chronic failure.

B) CHRONIC CONGESTIVE HEART FAILURE

In chronic congestive heart failure, manifestations of cardiac dysfunction appear insidiously and are *not evident at rest in mild cases*. History is extremely important for detection of mild cases characterized only by exertional dyspnea. In infants, exertional dyspnea leads to feeding difficulties but in children exercise intolerance is the main feature. In moderate cases, dyspnea becomes to mild exercise and manifestations of systemic congestion appear. In severe cases, dyspnea at rest and marked systemic congestion occur.

Clinical grading of chronic congestive heart failure

Grade I: Exertional dyspnea only
Infants: Feeding difficulty (small feeds, dyspnea with suckling).
Children: Exercise intolerance (walking, climbing stairs, sports).

Grade II: Exertional dyspnea and systemic congestion
Dyspnea to mild exertion (walking short distance).
Systemic congestion (hepatomegaly, distended neck veins, edema).

Grade III: Dyspnea at rest and severe systemic congestion
Rapid respiration at rest. Orthopnea and nocturnal dyspnea are common.
Severe congestion with ascites, ± hydrothorax.

- Exertional dyspnea is not peculiar to congestive heart failure but it also occurs with chronic chest diseases (as bronchial asthma) and chronic systemic illnesses.
- Chest x-ray, ECG and echocardiography are important to know that the dyspnea is due to cardiac disease and not chronic chest or systemic illness.
- Cor pulmonale should be always in mind as a possible cause of chronic congestive heart failure or cardiomegaly. Chronic upper airway obstruction (as hypertrophied adenoids) and chronic lung disease (asthma, cystic fibrosis) should be excluded.

Diagnosis of the cause of chronic failure requires consideration of the age, associated clinical findings and some investigations.

- In infants, congenital HD and congestive cardiomyopathy are the main causes.
- In children, congenital HD, chronic rheumatic heart disease and cardiomyopathy are the main causes.

7. Circulatory failure (Shock)

S: Septic shock or endotoxic shock (severe septicemia)
H: Hypovolemic shock (Dehydration, hemorrhage, burns)
O: Obstructive shock (Critical PS, critical AS, critical coarctation)
C: Cardiogenic shock (Acute CHF, acute tamponade, cardiac surgery, sepsis)
K: Kinetic or distributive shock (Anaphylactic, neurogenic, septic)

Other causes (Acute suprarenal failure, pancreatitis, pulmonary embolism)

Circulatory failure or shock is a serious life-threatening condition characterized by hypoperfusion of tissues. This hypoperfusion can result from decreased blood volume (hypovolemic), decreased myocardial contraction (cardiogenic), obstruction to blood flow (obstructive), venuolar and arteriolar dilatation (distributive) or combination of factors (septic).

Hypoperfusion of tissues is serious as it leads to tissue ischemia (hypoxia and substrate deficiency) and tissue damage. Initially, hypoperfusion is limited to nonvital organs (as skin) but with continued hypoperfuson, hypotension and hypoperfusion of vital organs occur. It is important to remember that *tissue hypoxia* (oxygen deficiency) can result from hypoxemia, anemia or shock but *tissue ischemia* (oxygen and substrate deficiency) results from shock only.

How to diagnose shock and what is the stage?

The best way for dealing with shock is through prevention or at least early detection before serious tissue injury occurs. Shock should be *suspected and expected* in all conditions known to lead to shock especially patients with gastroenteritis, high fever or heart failure. Early detection and early correction is the key for successful therapy.

Although there is no sharp demarcation between the several events occurring in shock, it is possible to divide shock into 4 stages with increasing severity.

Stages of shock	
I. Early shock	**Peripheral hypoperfusion** Tachycardia and poor peripheral perfusion.
II. Established shock	**Arterial hypotension** Tachycardia, poor peripheral perfusion and arterial hypotension.
III. Advanced shock	**Vital organ hypoperfusion** Multiple organ system failure (MOSF).
IV. Irreversible shock	**Irreversible cellular damage** Refractory metabolic acidosis.

1. Early shock: During this stage, clinical manifestations are related to the catecholamine release, which is a compensatory mechanism of the body to prevent the fall in blood pressure. These manifestations are tachycardia and poor peripheral perfusion (due to vasoconstriction). During this stage clinical manifestations of shock are usually overshadowed by the clinical manifestations of the cause (as diarrhea, high fever or heart failure). High index of suspicion is extremely important.

Clinical manifestations of peripheral hypoperfusion

Cold extremities and increased core-peripheral temperature difference.
Slow capillary refill over fingernails (refill in more than 5 seconds).
Skin mottling and peripheral cyanosis.

- Normal capillary refill occurs in less than 3 seconds.
- In septic shock, peripheral vasoconstriction is absent and on the contrary, peripheral perfusion is enhanced leading to "warm shock".

2. Establishing shock: With continued hypoperfusion and failure of compensatory mechanisms, hypotension occurs. The clinical triad of tachycardia, hypotension and peripheral hypoperfusion become evident. The patient looks pale and anxious.

3. Advanced shock: During this stage, hypoperfusion of vital organs occurs. Initially, selective redistribution of blood occurs where perfusion increases to most vital organs (brain, heart) at the expense of less vital organs (kidney, lungs and GIT). Manifestations of acute failure of several systems occur with a variable severity and different combinations.

Manifestations of multiple organ system failure (MOSF)

Kidneys	Acute renal failure (oliguria, metabolic acidosis).
Lungs	Adult respiratory distress syndrome (ARDS or shock lung).
GIT	Ischemia, stress ulcers, hemorrhage, ileus.
Blood	Disseminated intravascular coagulation (DIC).
Metabolic	Metabolic acidosis (due to anaerobic metabolism), electrolyte disturbance.
Brain	Hypoxic ischemic encephalopathy (disturbed consciousness).
Heart	Myocardial ischemia, serious arrhythmias.

- Clinical and laboratory evaluation of all these systems is essential.

4. Irreversible (refractory) shock: During this terminal stage, persistent tissue hypoxia and anaerobic metabolism will eventually lead to irreversible cellular damage (of mitochondria and cell membrane). Clinically, myocardial ischemia and brain ischemia are well evident (serious arrhythmias, deep coma). Metabolic acidosis is severe or profound and is refractory to therapy (pH is below 7.0 in spite of vigorous correction with sodium bicarbonate).

8. Cardiac Arrhythmias

Tachyarrhythmias	Bradyarrhythmias
Sinus tachycardia	**Sinus bradycardia**
Physiological	Physiological
Pathological	Pathological
Supraventricular tachyarrhythmia	**Atrioventricular block (AV block)**
Paroxysmal atrial tachycardia	First degree heart block
Atrial flutter	Second degree heart block
Atrial fibrillation	Third degree heart block
Ventricular tachyarrhythmia	**Sick sinus syndrome**
Ventricular tachycardia	
Ventricular fibrillation	**Asystole**

Extrasystoles (Premature beats)
Premature atrial contractions (PACs): Physiological or pathological
Premature ventricular contractions (PVCs): Physiological or pathological

Abnormalities in the rate and rhythm of the heart can be physiological or pathological, congenital or acquired, transient or chronic and benign or life-threatening. Electrocardiography (ECG) is essential for precise diagnosis.

A) TACHYARRHYTHMIAS

These disorders are characterized by a rapid heart rate due to rapid discharge from SA node, supraventricular or ventricular ectopic focus.

1. Sinus tachycardia: It is the commonest disorder, which is characterized by rapid discharge from the sinoatrial node (SA node). The condition may be *physiological* (anxiety, exercise, crying, pain) or *pathological* (fever, shock, hypoxia, heart failure, cardiac tamponade, anemia). *Drugs* as adrenaline, atropine and theophylline are also responsible.

- Clinically, tachycardia disproportionate to the age is the main finding. Clinical features of the cause are usually evident.
- ECG reveals fast heart rate with normal P wave, normal 1:1 AV conduction and normal QRS complex.
- As the condition represents a physiological compensatory mechanism, treatment should be only directed to the cause and not for slowing the heart rate.

2. Supraventricular tachycardias: In these conditions, the rapid heart rate is originating from an abnormal mechanism proximal to the bifurcation of the bundle of His.

a) Paroxysmal supraventricular tachycardia: It is caused by the "re-entry" phenomenon through the AV node or through accessory conducting tissue pathways such as the bundle of Kent or bundle of James. The atria are exited through the aberrant retrograde entry causing circular movements of depolarization.

• The paroxysm (or the attack) occurs suddenly without an evident cause and usually at rest. The heart rate is usually above 180/minute (180 - 300). Short attacks for minutes or hours are well tolerated by most children but prolonged or exceptionally severe attacks lead to acute congestive heart failure (tachycardia, tachypnea and hepatomegaly). Maneuvers that increase vagal tone (carotid sinus massage or firm abdominal pressure) may successfully terminate the attack and should be tried. The attack, as it begins suddenly, also terminates suddenly.

• ECG shows very rapid heart rate with normal P wave, normal 1:1 AV conduction and normal QRS complex.

• As the condition is life-threatening, immediate treatment is indicated.

b) Atrial flutter: This uncommon condition is characterized by an abnormal atrial focus discharging at a very rapid rate (300 - 500/minute) to which the atria respond leading to atrial saw tooth flutter waves. As AV node cannot transmit all these impulses, a certain degree of AV block occurs (the commonest is 2:1). Diagnosis is confirmed by ECG, which shows a rapid regular heart rate with saw tooth P waves and regular QRS complex. For each 2 - 3 P waves, there is one QRS complex (1:2 or 1:3 AV block). The condition is rare in normal heart but may occur in congenital or rheumatic heart diseases.

c) Atrial fibrillation: This condition is mostly seen in children with chronic rheumatic heart disease especially with mitral stenosis. It is characterized by an abnormal atrial foci discharging irregularly and ineffectively at an extremely rapid rate (350-600/minute) and result in disorganized and ineffective atrial contractions and variable ventricular response. Clinically, the cardiac rhythm is very irregular so that 4 successive regular beats cannot be counted. ECG shows absent P waves (irregular baseline), irregular R-R intervals (irregular ventricular contractions) but normal shaped QRS complex.

3. Ventricular tachycardias: In these conditions, the rapid heart rate is originating from an abnormal mechanism in the ventricles.

a) Ventricular tachycardia: It is a serious life-threatening arrhythmia, which may progress to the fatal ventricular fibrillation. The condition may occur with myocarditis, cardiomyopathy or digitalis toxicity. Shock, hypoxia, severe electrolyte disturbances are contributing factors. The condition may occur suddenly or may follow multiform premature ventricular contractions. Clinically, tachycardia is present and may lead to syncope or sudden death. ECG shows rapid and wide QRS complexes not preceded by P waves. Capture or fusion beats, if present, are diagnostic. Immediate treatment with I.V. lidocaine or phenytoin is essential before ventricular fibrillation occurs.

b) Ventricular fibrillation: This potentially fatal arrhythmia results in death unless immediate resuscitative measure within 4 minutes succeeded to restore ventricular beats. It may follow ventricular tachycardia or occur suddenly following severe anoxia, advanced shock or serious electrolyte disturbances. Clinically, the patient suddenly

becomes unconscious with no detectable heart beats (cardiac arrest). The ECG shows total disorganization with absent QRS complexes. Immediate cardiac compression, artificial ventilation, intracardiac adrenaline are necessary. Defibrillation (cardioversion) may be also needed. It is important to remember that cardiac arrest may indicate ventricular fibrillation or asystole (see below).

B) BRADYARRHYTHMIAS

These disorders are characterized by a slow heart rate due to slow discharge from SA node, AV block or other disorders of conduction.

For diagnosis of bradycardia, it is important to remember that the normal lower limit of heart rate varies with age. Bradycardia is a heart rate below this limit.

Normal lower limit of heart rate in awake children

Newborns	Infants	Young children	Old children
90/min.	100/min.	80/min.	60/min.

- During sleep, these limits are lower (50 for children and 60 for infants).

1. Sinus bradycardia: This condition is characterized by a slow discharge from the SA node leading to a slow heart rate. It may be physiological (during sleep, in athletes, in healthy individuals) or pathological (syncope, increased intracranial pressure or stressful procedures). Drugs as digoxin or propranolol may be responsible.

- Clinically, slow regular heart rate is the main finding. In extreme cases, congestive heart failure may occur or the condition may progress to asystole. The heart rate characteristically increases with exercise (or crying) and usually exceeds 100/minute. This is an important clinical differentiating point from patients with bradycardia due to AV block (see below).

- ECG reveals slow heart rate, normal P wave, P-R interval and QRS.

2. Atrioventricular block (AV block): Conduction block or delay at the atrio-ventricular level can be divided into 3 degrees

a) ***First degree AV block:*** It is characterized by a prolonged P-R interval. The rhythm is regular and all impulses are conducted.

b) ***Second degree AV block:*** It is characterized by failure of conduction of some, but not all, atrial impulses to the ventricles. It is divided into 2 types.

(i) *Mobitz type I (Wenckebach phenomenon)*: P-R interval becomes progressively longer until an atrial impulse is not conducted and a dropped beat occurs. This may occur over two, three, four or even five beats before nonconduction happens. The conduction delay occurs at the level of AV node.

(ii) Mobitz type II: It is characterized by intermittent irregular sudden dropping of beats not preceded by progressive P-R prolongation. It is more serious than type I because it frequently progresses to complete AV block. The level of conduction blockade is at the bundle of His.

c) Third degree AV block (complete heart block): No impulses from atria reach the ventricles and complete atrioventricular dissociation occurs (no constant relation between P waves and the slow QRS complexes). Complete heart block can be congenital or acquired. The prognosis of the congenital form is usually good. Digitalis toxicity is the most common cause of acquired cases.

3. Sick sinus syndrome: This arrhythmia mostly occurs following cardiac surgery but may also occur with myocarditis, myocardial ischemia or cardiomyopathy. It is characterized by periods of profound unresponsive sinus bradycardia with or without escape rhythms. These scape rhythms may give rise to periods of tachyarrhythmia, and hence, the name ***"bradycardia-tachycardia syndrome"***. In symptomatic patients, drug therapy or ventricular pacemaker is necessary.

4. Asystole: Complete cessation of cardiac contractions (flat ECG) may follow extreme bradycardias or occur with severe hypoxia, acidosis, shock, hypothermia, electrolyte disturbances or hypovolemia. Stressful procedures as intubation, lumbar puncture or I.V. insertion may also lead to cardiac arrest. Immediate resuscitative measures are life-saving.

C) EXTRASYSTOLES

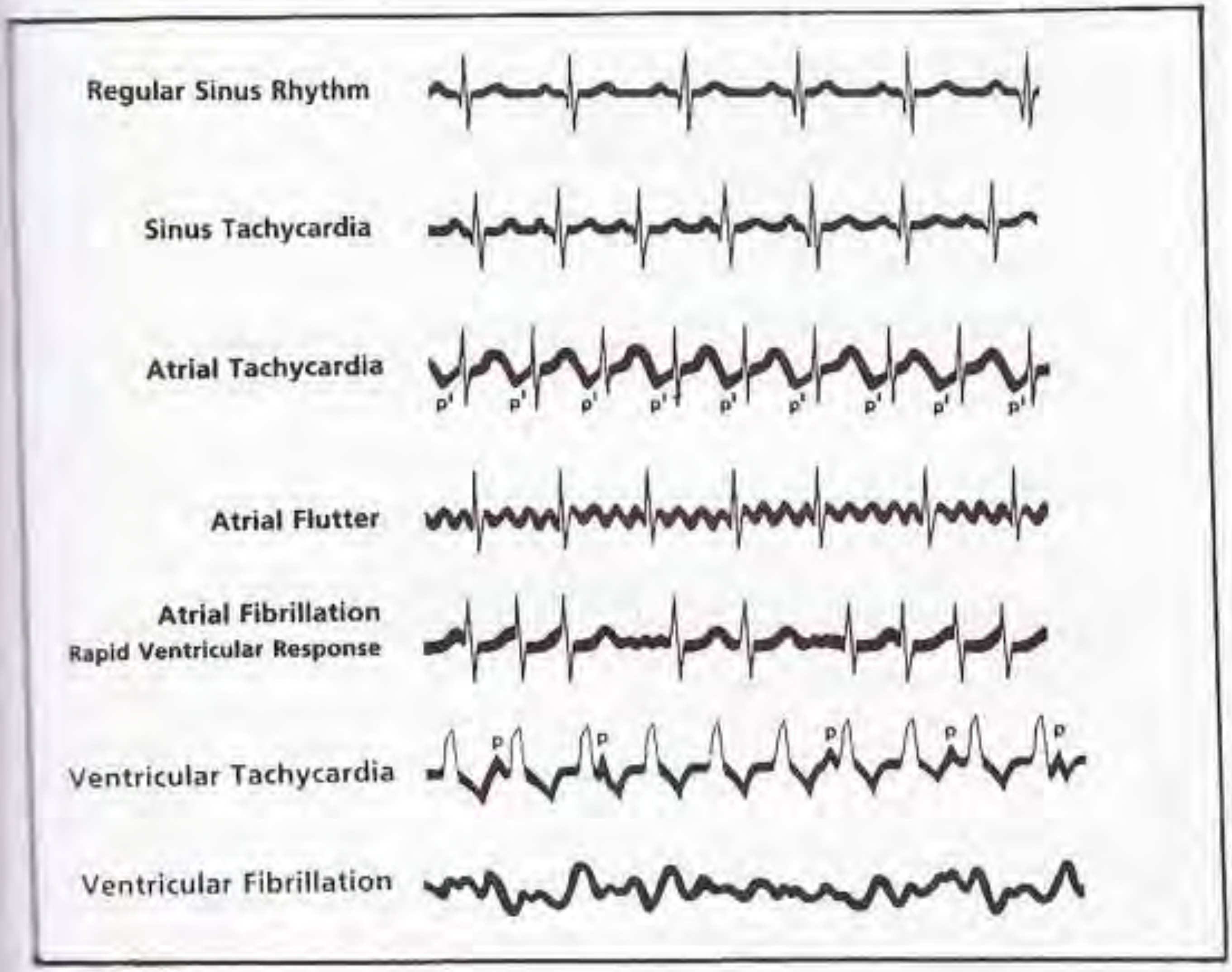
Extrasystoles or premature beats are mostly benign and present in normal individuals. However, they may also accompany an organic heart disease or occur with drugs especially digoxin. They occur due to a discharge from an ectopic focus present anywhere in the atrial, junctional or ventricular tissue and results in a premature beats.

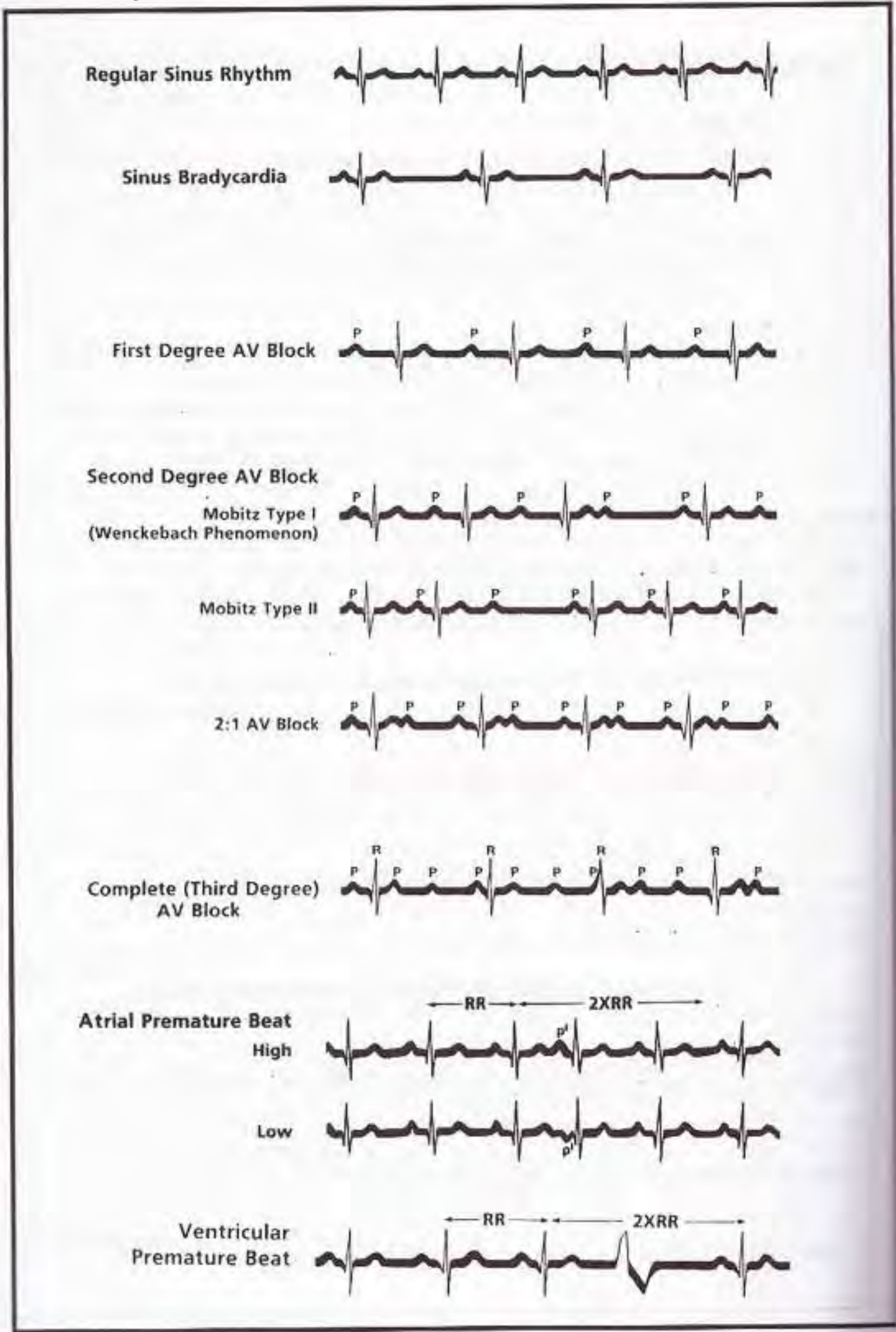
1. Premature atrial contractions (PACs): It is characterized by an abnormally shaped P wave that occurs prematurity. QRS complex is normal and there is no compensatory pause. Occasionally, the early P wave is blocked in bundle branches leading to wide QRS.

2. Premature ventricular contractions (PVCs): It is characterized by a wide and bizarre QRS, inverted T wave and a compensatory pause. There is no relationship between the normal P waves and the QRS complex. The extrasystole may take a definite rhythm, for example, alternating with normal beats (pulsus bigeminy) or occurring after 2 normal beats (pulsus trigeminy). Premature ventricular beats are usually benign unless they are: (1) Multiform (different QRS morphology), (2) Frequent (occurring without intervening sinus beats), (3) Prolonged QT interval, (4) R on T (premature ventricular beat occurring on the preceding T wave), (5) Increase with exercise or causing anxiety and (6) With underlying cardiac disease.

ECG changes in cardiac arrhythmias

Tachyarrhythmias	
Sinus tachycardia	Normal P wave, normal AV conduction, normal ORS.
Paroxysmal SVT	Normal P wave, normal AV conduction, normal ORS.
Atrial flutter	Saw tooth P wave, 2:1 or 3:1 AV block, normal QAS.
Atrial fibrillation	Absent P wave, irregular AV conduction, normal QRS.
Ventricular tachycardia	Wide QRS not preceded by P wave, ± fusion beats.
Ventricular fibrillation	Absent QRS, total disorganization.
Bradyarrhythmias	
Sinus bradycardia	Normal P-R interval, normal AV conduction.
First degree AV block	Prolonged P-R interval, normal AV conduction.
Second degree AV block	(Some, but not all, atrial impulses are not conducted).
Mobitz type I	Progressive prolongation of P-R interval, dropped beats.
Mobitz type II	Intermittent irregular sudden dropping of beats
Third degree AV block	All atrial impulses are not conducted (AV dissociation).
Extrasystoles	
Premature atrial Cs	Early abnormal P wave, normal QRS, no compensatory pause.
Premature ventricular Cs	Wide bizarre QRS, inverted T, compensatory pause.




Regular Sinus Rhythm
Sinus Bradycardia
First Degree AV Block
P
Second Degree AV Block
Mobitz Type I
(Wenckebach Phenomenon)
P
Mobitz Type II
P
2:1 AV Block
P
Complete (Third Degree)
AV Block
R
P
Atrial Premature Beat
High
Low
RR
2XRR
P'
Ventricular
Premature Beat
RR
2XRR

" بســـم الله الرحمن الرحيم "

7

* Respiratory System *

- **Respiratory System Examination.**

1. **Upper Respiratory Presentations.**
2. **Cough.**
3. **Stridor.**
4. **Wheezing.**
5. **Respiratory Distress.**
6. **Recurrent Chest Infection.**

Respiratory System Examination

Hearing of abnormal audible sounds
- Cough, noisy respiration

Examination of upper respiratory system
- Ear examination
- Nose examination
- Throat examination

Chest examination
- Inspection (Respiratory distress, diminished expansion, bulge or retraction)
- Palpation (Mediastinal shift, palpable rhonchi)
- Percussion (dullness, hyperresonance)
- Auscultation (Diminished air entry, abnormal breath sounds, adventitious sounds)

1. *Hearing of abnormal audible sounds*

Before actual examination, attention should be given to the presence of abnormal sounds as a lot of information can be gained through this simple step. These abnormal sounds include:

1. Cough: When it is the complaint, it is important to listen to the patient's cough to determine its characters (dry or productive, brief or spasmodic and if having special characters as metallic or coarse).

2. Noisy respiration: Hearing of audible noises (by naked ears) during respiration is a common clinical presentation denoting partial airway obstruction. Total airway obstruction results in cyanosis and death. The duration and character of the noise depends on the level of obstruction. High obstruction is associated with inspiratory noise while low obstruction produces expiratory noise.

Types of noisy respiration

Snoring	Inspiratory irregular sound produced by partial obstruction at the nasal, nasopharyngeal or oropharygneal level.
Stridor	Inspiratory continuous harsh sound produced by partial obstruction at the level of the larynx or trachea.
Rattling	Inspiratory (± expiratory) irregular coarse sounds produced by partial obstruction of trachea and major bronchi by secretions. These sounds can be also felt (palpable rhonchi) and auscultated.
Wheezing	Expiratory continuous musical sound produced by partial obstrucion at the level of the small bronchi and bronchioles. These sounds can be also auscultated.
Grunting	Early expiratory short sound produced by forced expiration against the closed Epiglottis. It is a sign of severe respiratory distress.

2. Examination of the upper respiratory system

Examination of the nose, ears and throat is extremely important and should not be overlooked. Infections in these areas are very common and may lead to serious complications.

3. Chest examination

1. Inspection: It is very useful for detection of the following:

a) Respiratory distress: It is essential to count the respiratory rate over one minute, to look for retractions (suprasternal, intercostal and subcostal) and to look for cyanosis and altered consciousness. Identification and grading of respiratory distress depend on these simple steps.

Grading of respiratory distress

Grade I (mid distress)	Rapid respiration and working alae nasi.
Grade II (moderate distress)	Intercostal and subcostal retractions.
Grade III (severe distress)	Expiratory grunting.
Grade IV (advanced distress)	Central cyanosis and disturbed consciousness.

b) Diminished chest expansion: Generalized poor expansion occurs with severe airway obstruction or with respiratory depression or paralysis. Unilaterally diminished expansion always reflects a focal pathology. With suspicion, auscultation reveals diminished air entry.

c) Unilateral bulge or retraction: Unilateral bulge occurs with pneumothorax or pleural effusion while unilateral retraction occurs with collapse or fibrosis. Any associated chest deformity should be also observed.

2. Palpation: It is important for detection of:

a) Mediastinal shift: Palpation of the trachea and apex beat is important. Mediastinal shift to the other side occurs with pneumothorax or pleural effusion while shift to the same side occurs with collapse and fibrosis.

b) Palpable rhonchi: Secretions in the major bronchi can be palpated over the chest. This is usually associated with productive cough and rattling sound. Resolving bronchitis or aspiration are the main causes.

3. Percussion: It is important for detection of:

a) Dullness: It mainly occurs with lobar or massive consolidation, massive collapse and pleural effusion. Auscultation reveals diminished air entry over the involved area.

b) Hyperresonance: It occurs in pneumothorax. It is usually associated with respiratory distress and mediastinal shift to the other side.

4. Auscultation: It is the most useful step in examination and the most reliable method for differentiation between different pulmonary diseases. It should include

auscultation of the front, sides and back. Comparison of both sides and corresponding areas is very important for detection of abnormalities. Auscultation is useful for detection of the following:

a) Diminished air entry: Generalized diminished air entry occurs with severe airway obstruction (as asthma) or with respiratory depression or paralysis. Unilaterally diminished air entry occurs with consolidation, effusion, collapse or pneumothorax.

b) Abnormal breath sounds: Normal breath sounds are vesicular. Abnormalities in breath sounds include:

(i) Harsh or rough vesicular sounds: In bronchitis.
(ii) Bronchial breathing: In consolidation or collapse.
(iii) Bronchophony: Increased vocal resonance especially during speech or crying due to enhanced transmission of sounds. It occurs with bronchial breathing.

c) Adventitious sounds: These abnormal auscultatory sounds include crepitations, rhonchi and wheezes.

• *Crepitations* are interrupted inspiratory sounds produced by passage of air through fluids. Fine crepitations usually indicate an alveolar or a small airway disease while coarse crepitations are mainly associated with secretions in the large airways.

Types and causes of crepitations

Fine crepitations	Coarse crepitations
With respiratory distress	**With respiratory distress**
Bronchopneumonia.	Pulmonary edema.
Acute bronchiolitis.	Aspiration pneumonia.
Bronchopulmonary dysplasia.	Organic phosphorus poisoning.
Acute heart failure.	Pulmonary hemorrhage.
Without respiratory distress	**Without respiratory distress**
Mycoplasma pneumonia (lobar).	Resolving bronchitis.
Bronchiectasis (basal).	Resolving pneumonia

•Crepitations can be heard in quiet or crying patient.

• *Rhonchi* are continuous coarse expiratory sounds produced by narrowing of the large bronchi by secretions. The main cause is bronchitis.

• *Wheezes* are continuous musical expiratory sounds, usually accompanied with prolonged expiration, produced by narrowing of the smaller airways (small bronchi and bronchioles) by inflammation (bronchiolitis), bronchospasm (asthma) or compression. As wheezing is an expiratory sound, it cannot be heard in crying patient because crying is also an expiratory sound.

1. Upper Respiratory Presentations

Nasal discharge	Earache (otalgia)	Sore throat
Common cold	Otitis media	Streptococcal pharyngitis
Allergic rhinitis	Otitis externa	Viral pharyngitis
Sinusitis	Other ear causes	Diphtheritic pharyngitis
Unilateral discharge	Furuncle	Infectious mononucleosis
Nasal diphtheria	Foreign body	Retropharyngeal abscess
Foreign body	Wax occlusion	Peritonsillar abscess
Infected polyp	Referred pain	Agranulocytosis

Infections of the nose, ear and throat are very common daily problems in pediatric practice. Although these infections are mostly simple and benign, several serious complications may occur:

- Common cold may be followed by acute bronchiolitis or bacterial pneumonia.
- Otitis media may lead to hearing loss or serious neurological complications.
- Streptococcal pharyngitis may lead to rheumatic fever or glomerulonephritis.

A) NASAL DISCHARGE

Nasal discharge (rhinorrhea) is probably the commonest presentation in pediatric practice. The discharge is frequently watery (running nose), but it may be mucoid, purulent or rarely bloody. The main causes are:

1. Common cold: Common cold is the commonest infection in children with an average of 6-7 colds per year in young children Other terms as "nasopharyngitis", "rhinitis" or "coryza" are also used. Unlike adults, the infection in infants and children usually involves the sinuses and nasopharynx, hence the name "nasopharyngitis". The illness is mostly viral in origin (rhinoviruses, coronaviruses and several other viruses) but bacterial infection also occurs (pneumococcal, staphylococcal, hemophilus influenza, pertussis and several other bacteria). The main clinical features are:

- ***Fever:*** The onset is usually sudden with low-grade fever, irritability and sneezing. Fever may be absent in older children. High fever should suggest complications as otitis media or sinusitis.
- ***Nasal discharge:*** It begins within few hours of onset. It is usually watery during the first few days, then it turns to mucoid for another few days. Nasal obstruction may be severe especially in infant, and it may interfere with feeding. It is important to emphasize that significant cough should not be accepted as a concomitant sign as it usually denotes an early tracheitis or bronchitis.
- ***The course*** is benign in the majority of cases. Fever subsides within 2 days and nasal discharge over a week. However, nasal discharge may remain as long as 2 weeks.

'It is more blessed to give than to receive.

• ***Complications:*** Common cold should not be taken lightly as it may be an early sign of a more serious coming disease. Complications should be considered in the presence of high fever, significant cough or persistent nasal discharge for more than 10 days.

Complications of common cold

Spread of infection to ears and sinuses (otitis media, sinusitis).
Tracheobronchitis or laryngotracheobronchitis.
It may be the prodromal stage of measles or whooping cough.
Precipitation of an asthmatic attack in asthmatic patient.
Serious lower respiratory infections (acute bronchiolitis, bacterial pneumonia).

- History of asthma in every case of common cold is important.
- Examination of eardrums to exclude otitis media is essential.
- Re-examination after few days to exclude serious infections is useful.

2. Allergic rhinitis: It is a common cause of recurrent watery nasal discharge. The suggestive clinical criteria for diagnosis are:

1. Watery nasal discharge unaccompanied with fever.
2. Prominent itching and sneezing.
3. History of allergy or presence of other allergic manifestations.
4. Pale nasal mucosa (congested in common cold).
5. Dramatic response to nasal decongestants.

3. Sinusitis: It is a common bacterial complication of common cold. The suggestive clinical criteria for diagnosis are:

1. Nasal discharge accompanied with high fever.
2. Purulent discharge or discharge persisting for more than 10 days.
3. Mid-sleep and early morning cough especially when the patient is not coughing during the rest of the day. This is due to the postnasal discharge.
4. Pain in the region of sinuses or painful percussion.
5. Throat examination reveals a thick purulent discharge drooping on the posterior pharyngeal wall.

- X-ray on sinuses may be also needed especially in chronic cases.
- Chronic sinusitis (persistent symptoms for more than 90 days) is an important cause of chronic cough.

4. Unilateral nasal discharge: It should suggest a focal lesion as nasal foreign body, infected polyp or nasal diphtheria. The discharge can be purulent, smelly or blood tinged. Careful examination of the nose is essential for diagnosis.

B) EARACHE (OTALGIA)

Painful ear or otalgia is a very common complaint in children. Infants and young children may demonstrate the pain by unexplained crying and irritability or by rubbing or pulling of the painful ear. The main causes of earache are:

1. Otitis media: Acute inflammation of the middle ear is a common complication of common cold especially in late infancy and early childhood (6 months to 6 years). The illness is mostly bacterial and can be caused by gram-positive or gram- negative bacteria. Two organisms (streptococcus pneumonia and hemophilus influenza) account for 50% of cases. Other common organisms are B. catarrhalis, streptococcus pyogens, staphylococcus aureus and pseudomonas aeruginosa. The clinical forms are:

a) ***Acute otitis media:*** The illness starts acutely, few days after the onset of common cold, with *fever and earache.* Common cold with high fever or with fever that recurs should raise suspicion. Also, any febrile patient with unexplained irritability or excessive crying should be examined for otitis media. *Ear discharge (otorrhea)* may occur with drum perforation. *Ear examination* with otoscope reveals a congested bulging eardrum. Purulent discharge may be also seen if perforation occurs. Immediate antibiotic therapy for at least 7 days is important to prevent complications.

b) ***Recurrent otitis media:*** Some children develop suppurative otitis media with almost every "common cold". Prophylactic antibiotic therapy in these children is effective (single daily dose of ampicillin or amoxicillin).

c) ***Secretory otitis media*** *(otitis media with persistent effusion):* Persistent middle ear effusion after 2 weeks of antimicrobial therapy is a common complication which is also called "serous otitis media" or "nonsuppurative otitis media". The main clinical presentation is *partial hearing loss* and not earache. Ear examination with otoscope reveals a dull, opaque and immobile eardrum and serous fluid in middle ear. The condition usually subsides within 6 weeks in most cases even without treatment.

Complications of otitis media

Ear complications

- Drum perforation (acute or chronic).
- Chronic suppurative otitis media (hearing loss).
- Chronic secretory otitis media (hearing loss).

Skeletal complications

- Acute or chronic mastoiditis: Swollen, painful and erythematous mastoid area.
- Petrositis: Infection of the pneumatized cells of temporal bone.

Neurological complications

- Meningitis or focal otitic encephatitis.
- Acute cerebral thrombophlebitis (acute hemiplegia).
- Acute labyrinthitis (acute ataxia).
- Acute facial palsy.
- Epidurat or subdural empyema.

2. Otitis externa (external otitis): Acute infection of the cartilaginous part of the external ear (outer two thirds in infants and outer third in children) can be caused by gram-positive or gram-negative bacteria. Fungal infection especially with candida is also common. The predisposing factors are excessive wetness (swimming, bathing).

dryness (dermatoses) or trauma to the external canal (finger manipulation or foreign body). The most evident clinical feature is an *ear pain*, which is accentuated by manipulation of the ear lobule or by pressure on the tragus (characteristic). *Scanty ear discharge* may be also present. *Ear examination* with otoscope reveals congestion and edema of the external canal. Eardrum is normal.

3. Other ear causes: Foreign body or furuncle in the external canal is also associated with earache and occlusion of the ear canal by cerumen produces hearing loss and may be earache.

4. Referred pain: Infections of the nose, mouth or throat may cause referred pain to ears. Ear examination reveals no abnormality.

C) SORE THROAT

Sore throat is a common complaint in pediatric practice, which is mostly caused by acute infections of the pharynx and tonsils (pharyngotonsillitis). Young children manifest throat pain by difficult swallowing or refusal of feeding. The main causes are:

1. Streptococcal pharyngitis: It is a common infection, which occurs in children above the age of 3 years with peak incidence between 4 - 7 years.

- The onset is usually *abrupt with high fever*; vomiting and abdominal pain and the condition may simulate acute appendicitis (see abdominal pain).
- Sore throat may be *severe* to a degree that makes swallowing difficult.
- Throat examination reveals diffuse redness of the tonsils and anterior pillars. Follicular exudation *(follicular tonsillitis)* or membranous exudation *(membranous tonsillitis)* are common and usually involving both tonsils. The membrane is limited to tonsils and does not extend to the adjacent areas.
- Tender anterior cervical lymphadenitis is an early common finding.
- Fever usually remains for 1- 4 days. In severe cases, it may persist for one week or even 10 days.
- Early complications as peritonsillar abscess may occur. Late autoimmune complications as rheumatic fever or poststreptococcal glomerulonephritis may occur in susceptible children.

2. Viral pharyngitis: It is by far the most common cause of acute pharyngitis in children. Infection in infants less than 1 year of age is uncommon.

- The onset is usually *acute with mild to moderate fever*. Rhinitis, cough, conjunctivitis or hoarseness are common associated findings that help in differentiation between streptococcal and viral pharyngitis.
- Sore throat is *moderate* and usually occurs 1 - 2 days after onset.
- Throat examination reveals mild erythema of tonsils and pillars. Small ulcers on the soft palate or posterior pharyngeal wall may occur. Follicular or membranous tonsillitis is rare.
- Cervical lymphadenitis is common. The nodes are moderately enlarged and usually slightly tender.

- The entire illness is short. Complete recovery occurs within 1 - 4 days.
- It is important to remember that total leukocytic count is not useful in differentiation between streptococcal and viral pharyngitis because in both conditions polymorphonuclear leukocytosis is common.

3. Diphtheritic pharyngitis: With the current routine vaccination, diphtheria became a rare disease. Unvaccinated children are at great risk.

- The onset is usually *insidious with mild fever*, anorexia and malaise.
- Sore throat is usually *not severe*.
- Throat examination commonly reveals a *gray membrane*, which is not limited to tonsils but usually extends to anterior pillars, soft or hard palate. In severe cases it extends to posterior pharyngeal wall and larynx (laryngeal diphtheria) leading to laryngeal obstruction and stridor. The membrane is adherent and trials of removal are followed by bleeding.
- Cervical lymphadenitis is common. In severe cases, edema of soft tissues of the neck occurs and gives the appearance of *"bull neck"*.
- In mild cases, recovery occurs in 1- 2 weeks. In severe cases serious or even fatal complications occur.
- Early diagnosis and immediate therapy are important. Material from the membrane should be examined microscopically, then cultured.

Complications of diphtheria

Laryngeal diphtheria
- Leads to stridor, which may cause total obstruction and death.

Toxic myocarditis
- Usually in the second week. Present in 70% of cases (only 15% are symptomatic).
- May lead to congestive heart failure or heart block.

Toxic neuropathy
- Usually after 2 -4 weeks of onset.
- Leads to acute paralysis (bilateral, motor, descending and transient).

4. Infectious mononucleosis: It is a viral disease caused by Epstein-Barr virus, which is a member of herpes group. As the infection principally involves the B lymphocytes (mononuclear cells), the term infectious mononucleosis is used.

- The onset is usually *insidious with mild to moderate fever*, headache and general weakness. These initial symptoms usually remain for 1 - 2 weeks before the appearance of other manifestations.
- Sore throat appears gradually and is usually *moderate to severe*.
- Throat examination reveals a picture, which may simulate streptococcal pharyngitis (with follicular or membranous tonsillitis).
- The most charactertistic signs are lymphadenopathy and hepatosplenomegaly. *Lymphadenopathy* is mainly involving the posterior cervical nodes but generalized

lymphadenopathy is also common. *Splenomegaly* occurs in 50% of cases and is usually not massive, while *hepatomegaly* occurs in only 30% of cases. In some cases, *maculopapular rash* may appear especially with ampicillin therapy (80% of cases treated with ampicillin develop a rash).

• The course of illness is prolonged over 3-6 weeks and the condition should be considered in the differential diagnosis of unexplained prolonged fever.

The 5 major clinical manifestations of infectious mononucleosis

Prolonged fever.
Sore throat.
Posterior cervical lymphadenopathy.
Splenomegaly, hepatomrgaly or both.
Maculopapular rash.

• *Complications* as myocarditis, interstitial pneumonia or hepatitis may occur. Neurological complications as ataxia or convulsions may also occur. Splenic rupture is the most serious complication and it usually related to mild trauma.

• *Laboratory diagnosis* depends on the presence of absolute lymphocytosis and atypical lymphocytes (activated T lymphocytes). Serological tests for Epstein-Barr virus are important for diagnosis (Monospot test and Paul-Bunnell test). It is interesting to note that although the infection is principally involving the B lymphocytes, the present lymphocytosis and the atypical lymphocytes are belonging to the T lymphocytes.

• Suggestive clinical features of infectious mononucleosis with absent serological evidence of Epstein-Barr virus should suggest one of 5 other possibilities known as "infectious mononucleosis-like illness". All these illnesses can be diagnosed by appropriate serological tests.

The 5 main causes of infectious mononucleosis-like illness

Heterophil negative infectious mononucleosis (especially in children under 5 years).
Cytomegalovirus infection.
Toxoplasmosis.
Acute viral hepatitis (especially hepatitis A).
Acute human immunodeficiency virus (HIV) infection or AIDS.

5. Other causes: ***Peritonsillar abscess*** and ***retropharyngeal abscess*** are usually associated with severe sore throat, high fever and marked swelling of the tonsillar tissue or posterior pharyngeal wall. ***Herpangina*** should be also considered in presence of one or more ulcers on the anterior pillars (see painful oral lesions). ***Agranulocytosis***, although uncommon, should be also considered as a cause of severe sore throat.

2. Cough

Acute cough	Chronic cough
Acute transient cough	**In infancy**
Acute bronchitis	Recurrent aspiration
Acute laryngitis	Anatomical lung abnormalities
Acute bronchiolitis	Physiological lung abnormalities
Acute pneumonia	Trachoebronchial compression
Acute asthmatic attack	Inherited immunodeficiency
Acute prolonged cough	**In childhood**
Complicated bronchitis	Chronic asthma
Chronic sinusitis	Chronic infections
Pertussis	Chronic irritation
Pertussis-like illnesses	Idiopathic pulmonary diseases
Interstitial pneumonia	Pulmonary infiltration

Foreign Body inhalation should be always in mind as a possible cause of acute, Chronic or recurrent cough

Cough is among the most common complaints in pediatric practice, which indicates an underlying respiratory pathology. It can be acute or chronic and isolated or associated with other presentations as noisy respiration or respiratory distress. Clinically, when cough is the main presentation, careful analysis of the complaint and listening to the cough sound can provide several useful information.

- What is the duration of cough?
- What are the characters of cough?
- What is the cause?

1. What is the duration of cough?

Cough with duration less than two weeks is considered acute. Duration between 2 weeks and up to 2 months can be called "prolonged cough". Chronic cough is considered when cough persists more than 2 months.

2. *What are the characters of cough?*

Several useful information can be gained through listening to the cough sound. In older children, the patient can be asked to cough but in infants and young children, stimulation of the posterior pharyngeal wall by a tongue depressor at the end of examination will induce cough. The following points are clinically significant:

- **Is it dry or productive?** Dry cough occurs with early infections especially tracheitis while productive cough occurs with bronchitis, resolving pneumonia, aspiration or bronchiectasis.

- **Is it brief or spasmodic?** Spasmodic (or paroxysmal) cough is a series of more than 5 coughs that occur during one expiration. It occurs with pertussis, pertussis-like illnesses, foreign body inhalation, severe tracheitis and interstitial pneumonias.

- **Is it having a special sound?** The sound of cough can provide useful information regarding the site or the origin of cough.

- Bovine or barking (croupy) cough: It occurs with laryngitis.
- Dry metallic (brassy) cough : It occurs with tracheitis.
- Tight (wheezy) cough: It occurs with bronchiolitis or bronchial asthma.

It is important to remember that in both laryngitis (without stridor) and tracheitis, chest examination does not reveal any abnormality and the only way for diagnosis and differentiation is through listening to the cough sound.

- **Is it having a certain time of occurrence?** The timing is also important.

- Nocturnal cough: Bronchial asthma, pertussis and pertussis-like illnesses.
- Midsleep and early morning cough: Sinusitis.
- Most severe on awakening in the morning: Chronic bronchitis or bronchiectasis.
- With exercise: Exercise-induced asthma.

3. What is the cause?

It is very important to remember than **foreign body inhalation** is a possible cause in every case of cough especially when (1) the onset is sudden, (2) accompanied with choking and (3) not preceded or associated with any illness. Foreign body inhalation is most common in late infancy and early childhood (6 months - 4 years), the age at which children put objects on their mouths. The most common inhaled objects are foods (as peanuts) and small objects (as buttons, beads, coins, safety pins). Clinical manifestations depend on the nature of the foreign body, location and degree of airway obstruction. Direct laryngoscopy and bronchoscopy are essential for diagnosis.

Clinical presentations of foreign body inhalation

Laryngeal foreign body
Croupy spasmodic cough, hoarseness, laryngeal stridor.

Tracheal foreign body
Cough, suprasternal retraction, audible expiratory slap and palpable thud.

Bronchial foreign body: (manifestations depend on the degree of obstruction).
Mild obstruction: Acute, prolonged or chronic cough. Recurrent chest infection.
Moderate obstruction: Intractable wheezing. Recurrent attacks of wheezy chest.
Severe obstruction: Unilateral or lobar obstructive emphysema (diminished air entry).
Complete obstruction: Unilateral or lobar collapse (diminished air entry).

A) ACUTE COUGH

Most cases of acute cough, unaccompanied with respiratory distress, can be diagnosed clinically with no need for chest x-ray or any investigations. With prolonged acute cough (duration more than 2 weeks), chest x-ray is indicated in addition to simple tests as CBC, CRP and ESR.

(a) Acute transient cough

1. Acute bronchitis: It is by far the most common cause of acute cough in children. The illness can be viral or bacterial and nonspecific or specific to certain diseases. ***Nonspecific*** bronchitis is mostly *viral,* following common cold, but *bacterial* infections (pneumococci, streptococci, staphylococci, hemophilus influenza) also occur especially in early infancy, with malnutrition and with immunodeficiency. ***Specific*** bronchitis occurs with measles, pertussis, diphtheria, scarlet fever and typhoid fever.

• The illness is mostly preceded by common cold 3 - 4 days before the onset.

• The onset is gradual with dry cough and chest burning or discomfort. Fever is common in young children but it may be absent. Persistent high fever should suggest a bacterial origin.

• The course of illness can be divided into 3 stages, each for few days:

- During the first few days *(early stage),* the cough is dry, severe, metallic (brassy) and may be spasmodic (tracheitis). Paroxysms of cough may be followed by vomiting (post-tussive vomiting). During this stage, chest examination is unrevealing and diagnosis depends entirely on the character of cough.

- During the next few days *(productive stage),* cough becomes productive and less severe and the chest becomes rattling. Chest examination reveals palpable rhonchi, rough breath sounds, expiratory rhonchi and moist crepitations.

- During the last few days *(convalescent stage or stage of resolution),* cough decreases in frequency and severity and chest signs disappear gradually.

• It is not unusual for simple bronchitis to remain as long as two weeks. Prolongation for more than 2 weeks suggests the presence of complications (see acute prolonged cough).

• Differentiation between bacterial and viral bronchitis is practically important. Bacterial infection is considered if the fever is high or persistent, patient looks sick, sputum is purulent and/or cough is prolonged. Laboratory confirmation can be made by CBC (polymorphonuclear leukocytosis), ESR (raised) and CRP (raised).

2. Acute laryngitis: When acute laryngitis is mild or occurring in older children, stridor is usually absent and the illness presents with hoarseness of voice and barking (croupy) cough. In this situation, diagnosis depends entirely on the character of cough.

3. Acute bronchiolitis: Although most cases of acute bronchiolitis present clinically with respiratory distress and wheezy chest, mild cases can present with fever, cough, auscultatory wheezing and minimal distress (see wheezing).

4. Acute pneumonia: Although most cases of pneumonia in infants and young children present clinically with respiratory distress, certain pneumonias can present with fever and cough, with minimal or no distress, especially in older children. The most important 2 examples are viral bronchopneumonia (fine bilateral crepitations without distress) and mycoplasma lobar pneumonia (lobar consolidation with fine crepitations limited to one lobe). Mycoplasma pneumonia is frequently overlooked by physicians and commonly misdiagnosed as bronchitis (see pneumonias).

5. Acute asthmatic attack: Mild acute asthmatic attack presents clinically with cough, expiratory wheezing and minimal or no distress. The attack can be precipitated by common cold or viral bronchitis (asthmatic bronchitis). History of asthma is important in every case of common cold or cough whether acute or chronic. (See bronchial asthma).

• Again, **Foreign body inhalation** should be considered if the onset is sudden, accompanied with choking and not preceded or associated with any other manifestations of infection.

(b) Acute prolonged cough

Cough persisting for more than 2 weeks should be taken with some concern. Although the diagnosis can be clinically made in most cases, simple investigations as chest x-ray, CBC, ESR and CRP are indicated and can provide useful information. The main causes are:

1. Complicated bronchitis: Persistence of cough for more than 2 weeks in bronchitis should raise several possibilities:

1. Secondary bacterial infection (bacterial bronchitis or pneumonia).
2. Associated sinusitis: Cough is mainly occurring during sleep (see below).
3. Presence of segmental collapse or localized obstructive emphysema. These complications should also suggest foreign body inhalation.
4. Post-infection transient hypersensitivity of cough receptors: This condition may follow severe viral infections. It is characterized by persistence of cough for few weeks with absence of any chest signs. Associated transient bronchial hyper-reactivity and wheezing may also occur.

• Identification of the cause depends on proper history, careful examination and simple investigations especially chest x-ray (collapse, consolidation, emphysema) and CBC and CRP (for bacterial infection).

2. Chronic sinusitis: Persistent or chronic sinusitis is a common cause of persistent nasal obstruction, nasal discharge and prolonged or chronic cough.
• The patient is usually afebrile and the cough characteristically occurs during sleep and in the early morning due to the accumulated postnasal discharge. The cough is almost absent during the rest of the day and chest examination is essentially free.
• Diagnosis depends on throat examination, which demonstrates the postnasal discharge drooling on the Posterior pharyngeal wall. Recurrent bronchitis is a common complication (sinobronchitis). X-ray on sinuses may show opacification. A search for predisposing factors as nasal polyps or infected adenoids is important.

3. Pertussis (whooping cough): It is a bacterial disease caused by bordetella pertussis. With compulsory vaccination in infancy, the disease has become relatively uncommon. However, the possibility of pertussis should be considered if the cough increases in severity and frequency during the second week of illness and becomes more at night.

- In classic cases, the course of illness can be classified into 3 stages:

a) Catarrhal stage (1-2 weeks): It starts with common cold, fever and cough, which increases gradually in frequency and severity and becomes more at night especially during the second week. Chest examination is usually free. It is important to emphasize that spasmodic cough with duration of illness less than 7-10 days is *not* due to whooping cough but usually due to severe bronchitis. In whooping cough, spasmodic cough does not appear before 10 - 14 days of onset.

b) Paroxysmal stage (2 -4 weeks): This stage is characterized by paroxysmal attacks of severe spasmodic cough characteristically more at night. The attacks are precipitated by activity, excitement or change in temperature. During an attack, a series of forceful cough (5-10) during one expiration occurs and the patient appears to struggle with congested face or cyanosis. The attack ends with sudden forceful inspiratory crow (whoop) and followed by vomiting or cough of large amount of thick mucoid sputum. The whoop may be absent but the post-tussive vomiting is characteristic.

c) Convalescent stage (1-2 weeks): During this stage, the number and severity of paroxysms decrease and vomiting becomes less frequent. Mild infection (as common cold) may return the cough to a point resembling new attack.

- Complications as pneumonia, collapse or pneumothorax are common in infants and young children with severe disease. Otitis media is also common and activation of a latent tuberculosis may occur. Hypoxic convulsions may occur during severe paroxysms. Mortality rate is high in infants.

- Clinical diagnosis is not difficult in classic cases. Laboratory confirmation depends on the presence of leukocytosis (above 20.000) with absolute lymphocytosis. Naso-pharyngeal swabs for culture or serological tests can be made in doubtful cases.

- Pertussis-like illness in properly vaccinated infants or children should suggest other causative agents especially adenovirus infection. In this situation, lymphocytosis is also present but usually not marked as in pertussis (see below).

4. Pertussis-like illnesses: Adenovirus, mycoplasma pneumonia and chlamydia trachomatis can produce a "pertussis-like illness" which cannot be differentiated from whooping cough. The possibility should be considered in properly vaccinated infants and children. Fortunately, pertussis, mycoplasia and chlamydia all respond to erythromycin.

5. Interstitial pneumonias: Viral interstitial pneumonias are characterized by spasmodic cough and prolonged course over several weeks. Clinically, respiratory distress may be present and chest examination reveals minimal signs (see pneumonias). Diagnosis depends on the chest x-ray, which reveals a reticulonodular or parahilar-peribronchial infiltrate (see Basic Pediatric Radiology).

Causes of prolonged cough with free chest examination

Post-infection transient hypersensitivity of cough receptors: Sputum contains macrophages.
Chronic sinusitis: Postnasal discharge on posterior pharyngeal wall.
Pertussis and pertussis-like illnesses: Characteristic clinical picture.
Interstitial pneumonias: Characteristic chest x-ray.

B) CHRONIC COUGH

As with any other chronic complaint, identification of the cause can be very difficult. Detailed history, meticulous examination and some investigations are all essential for diagnosis.

- Is it truly a chronic cough?
- Is it chronic benign or chronic serious illness?
- What is the cause?

1. *Is it truly a chronic cough?*

The complaint of cough for more than 2 months requires careful analysis. In many patients, the cough is not truly chronic but the condition represents two or more separate unrelated acute bronchitis with cough-free periods in between. Occasionally, the second infection may occur before complete recovery from the first illness. In this situation, history can reveal a period of partial improvement.

2. *Is it chronic benign or chronic serious illness?*

With true chronic cough, it is important to know whether the illness is benign or represents a chronic serious illness. History of prolonged fever, poor activity, weight loss or chronic purulent sputum usually indicate a serious illness. On examination, presence of clubbing of fingers, respiratory distress, persistent wheezing or crepitations on repeated examination also indicate a chronic serious illness. If none of all above features are detected, the chronic respiratory illness is usually benign.

3. *What is the cause?*

Identification of the cause of chronic cough can be very difficult and a diagnostic approach is usually needed to reach the diagnosis. This includes history, examination and some investigations (see below).

(a) Causes in infancy

1. Recurrent aspiration: *Aspiration related to feeding should suggest* gastro-esophageal reflux, H-type of tracheoesophageal fistula or cricopharyngeal incoordination. Barium swallow under screen can differentiate between them.

Diagnostic approach of chronic cough

History

Careful analysis of the characters of cough (see above).
Initial history suggesting foreign body (as sudden spasmodic cough and choking).
History of asthma (recurrent wheezing) or any other allergic conditions.
History of aspiration related to feeding.
History of chronic nasal obstruction suggesting sinusitis.
History of chronic diarrhea suggesting cystic fibrosis, tuberculosis or IgA deficiency.
History of chronic inhalation of irritants especially tobacco smoke.
History of gradual progression of symptoms suggesting a chronic progressive disease.
Family history of tuberculosis or any similar condition.

Examination

Throat examination may reveal purulent postnasal discharge (sinusitis).
Clubbing of fingers mostly indicates bronchiectasis.
Anemia suggests chronic infection or hemosiderosis.
Expiratory wheezing suggests asthma or several other possibilities (see wheezing).
Fine basal crepitations suggest bronchiectasis.
Coarse crepitations suggest chronic infection or aspiration.

Investigations

CBC, ESR and CRP: In ALL cases. May reveal infection or eosinophilia (asthma).
Chest x-ray: In ALL cases. May reveal hyperinflation or pulmonary infiltrate.
* Hyperinflation: Bronchial asthma, cystic fibrosis, alpha one antitrypsin deficiency.
* Pulmonary infiltrate (see Basic Pediatric Radiology).

Sputum examination: Color, odor, microscopic examination and culture.
Tuberculin test: With suspected tuberculosis.
Further investigations if the cough does not respond to initial therapeutic measures.
- CT scan of the chest (very important).
- Bronchoscopy for anatomical abnormalities or foreign body.
- Immunological study especially for secretory IgA deficiency.
- Sweat chloride test for cystic fibrosis.
- Serum level of alpha one antitrypsin.
- Radiological study for gastroesophageal reflux or tracheosophageal fistula.
- Evaluation of ciliary morphology and function for immotile cilia syndrome.
- Lung biopsy for diagnosis of chronic idiopathic pulmonary diseases (see below).

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2. Anatomical lung abnormalities: Tracheomalacia or bronchomalacia can lead to chronic cough. Bronchopulmonary dysplasia following severe neonatal lung disease or prolonged mechanical ventilation is an important cause.

3. Physiological lung abnormalities: Cystic fibrosis, alpha one antitrypsin deficiency and immotile cilia syndrome (or primary cilia dyskinesia) should be considered especially when positive family history is present.

4. Tracheobronchial compression: External compression of tracheobronchial tracts by vascular rings or lung cyst can lead to chronic cough or chronic wheezing. Acquired compression by enlarged nodes or tumors may be also responsible.

Vascular rings

Type	Frequency	Symptoms
Complete rings		
Double aortic arch	40%	Respiratory difficulty in infancy
Right aortic arch with left ligamentum arteriosum	30%	Swallowing dysfunction or mild respiratory symptoms after infancy
Incomplete rings		
Aberrant right subclavian artery	20%	Mild swallowing dysfunction
Anomalous innominate artery	10%	Respiratory difficulty in infancy
Anomalous left pulmonary artery	Rare	Respiratory difficulty since birth

- Respiratory difficulty include chronic stridor, chronic cough or chronic wheezing.
- Diagnosis is made by barium swallow, Doppler echocardiography or MRI.

5. Inherited immunodeficiency: Unusually severe, recurrent or persistent chest infection in infancy should raise the possibility of immunodeficiency. Secretory IgA deficiency is particularly important (see recurrent chest infection).

(b) Causes in childhood

1. Bronchial asthma: Some asthmatic children present clinically with chronic night cough and without evident wheezing (see asthma). History is important and a therapeutic trial with one of asthma controllers may be needed (See Practical Pediatric Therapy).

2. Chronic infections: Chronic sinusitis, tuberculosis and bronchiectasis are the most important (See recurrent chest infection). Chronic viral or fungal infections may be also considered.

3. Chronic irritation: Chronic inhalation of irritants especially tobacco smoke should be always considered as an important cause of chronic cough.

4. Chronic idiopathic pulmonary diseases: There are several rare pulmonary diseases, of unknown etiology, characterized by chronic cough, hemoptysis, progressive deterioration of pulmonary functions and pulmonary infiltrate. They include pulmonary hemosiderosis, pulmonary hemangiomatosis, diffuse interstitial fibrosis of the lung (Hamman-Rich syndrome), pulmonary alveolar proteinosis and pulmonary alveolar microlithiasis. CT scan of the chest is very helpful. Definitive diagnosis requires lung biopsy.

5. Pulmonary infiltration: Visceral larva migrans, leukemia, lymphoma, histiocytosis or Wilms tumor are occasionally responsible.

3. Stridor (Upper Airway Obstruction)

Acute stridor	Chronic stridor
Infectious croup	**Congenital chronic stridor**
Acute laryngitis (viral)	Laryngomalacia (commonest)
Spasmodic laryngitis	Tracheomalacia
Laryngotracheobronchitis	Laryngeal web
Acute bacterial tracheitis	Laryngeal tumor or cyst
Acute bacterial epiglottitis	Laryngeal compression (congenital)
Other causes	**Acquired chronic stridor**
Laryngeal diphtheria	Laryngeal stenosis
Laryngeal foreign body	Tracheal stenosis
Laryngospasm	Laryngeal tumors
Laryngeal edema (allergy, postextubation)	Laryngeal paralysis
Laryngeal compression (acute)	Laryngeal compression (acquired)

Stridor is a continuous inspiratory harsh sound produced by *partial obstruction* in the region of the larynx or trachea. Total obstruction leads to cyanosis and death.

- What is the degree of upper airway obstruction?
- What is the cause?

1. *What is the degree of upper airway obstruction?*

Clinical assessment of the degree of upper airway obstruction is very important for the decision regarding the place and line of management.

Clinical grading of stridor

Grade I (Exertional stridor)
Stridor appears only during crying or with exercise.

Grade II (Continuous stridor or stridor at rest)
Stridor is present at rest and becomes worse with exertion.
Infants below the age of one year should be hospitalized.

Grade III (Stridor with retractions)
Stridor is continuous and accompanied with suprasternal and supraclavicular retractions.
The patient looks anxious, irritable and struggling for breathing.
Hospitalization is indicated for all cases.

Grade IV (Stridor with cyanosis)
In addition to continuous stridor and retractions, cyanosis and altered consciousness occur denoting severe respiratory failure.
Urgent hospitalization and endotracheal intubation are indicated.

2. *What is the cause?*

Stridor can be acute or chronic. With acute stridor, the onset is abrupt or acute and the duration of illness is short (less than a week). With chronic stridor, the onset is rather gradual and the illness is extending over weeks or months. Acute stridor is much commoner and is life-threatening.

A) ACUTE STRIDOR

Most cases of acute stridor are caused by common viral or bacterial infections of the larynx or trachea (infectious croup). However, other causes should be in mind and should be routinely excluded.

(a) Infectious croup

Five clinical entities with increasing severity are recognized (3 viral and 2 bacterial). ***Viral infections*** are commoner and are usually milder. Parainfluenza viruses are the principal agent but other viruses as influenza, adenovirus or respiratory syncitial virus may be responsible. With ***bacterial infections***, fever is high and airway obstruction is severe. Staphylococcus aureus (acute tracheitis) and hemophilus influenza type b (acute epiglottitis) are the 2 main causative bacteria.

1. Acute infectious laryngitis: It is a common viral infection, which occurs mainly in children between 1-3 years. The illness starts with mild fever, rhinitis and croupy cough. Stridor appears 1-2 days later and is usually *mild to moderate*. Symptoms usually subside over few or several days.

2. Spasmodic laryngitis: It is a viral or probably allergic condition characterized by an attack of croupy cough and stridor that occurs principally at night. Stridor is usually *moderate* in severity and only lasts for several hours. The attack may be repeated at the nights of the second and third days but is usually milder. Recurrences may occur.

3. Laryngotracheobronchitis: It is a common potentially serious viral infection, which mainly occurs in children below 3 years. The illness starts with mild to moderate fever, rhinitis and brassy cough. Stridor appears 1 - 2 days later and is usually *moderate to severe* and *both inspiratory and expiratory* (characteristic). Chest examination reveals diminished air entry, prolonged expiration and expiratory rhonchi. Symptoms usually subside over 3 - 7 days but cough may remain longer.

4. Acute bacterial tracheitis: It is a serious bacterial infection mainly caused by staphylococcus aureus and principally occurs in children below 3 years. The illness starts with high fever and *gradually progressing stridor*. Airway obstruction becomes severe and the illness simulates acute epiglottitis, but direct laryngoscopy reveals normal epiglottis. Polymorphonuclear leukocytosis is usually present.

5. Acute bacterial epiglottitis: It is a very serious bacterial infection mainly caused by hemophilus influenza type b and principally occurs in children above 3 years

(3 - 7 years). The illness starts abruptly with high fever and *rapidly progressing stridor.* Airway obstruction becomes severe within hours. Cyanosis and death rapidly occurs if urgent endotracheal intubation is delayed. Direct laryngoscopy reveals large edematous cherry red epiglottis with intense inflammation around. Polymorphonuclear leukocytosis is usually present.

Clinical differentiation between the 5 types of infectious croup

Disease	Age	Fever	Stridor
Acute laryngitis	1 - 3 years	Mild	Mild
Spasmodic laryngitis	1 - 3 years	Absent	Moderate (at night)
Laryngotracheobronchitis	1 - 3 years	Mild to moderate	Moderate to severe
Acute tracheitis	Below 3 years	High	Severe (slow progression)
Acute epiglottitis	Above 3 years	High	Severe (rapid progression)

- Laryngotracheobronchitis is the only one with inspiratory and expiratory stridor.

(b) Other causes

Other five conditions should be also considered in case of acute stridor.

1. Laryngeal diphtheria (diphtheritic croup): Although it is a rare cause, it should be considered especially in infants with severe stridor. As the illness usually occurs due to extension from a pharyngeal focus, throat examination reveals a *tonsillar membrane.* Fever is usually mild but toxemia is evident and cervical lymph nodes are enlarged. Direct laryngoscopy reveals edema, congestion and a pseudomembrane. Culture from the membrane is essential for diagnosis.

2. Laryngeal foreign body: Although it is not a common cause, it should be considered when the *onset is sudden* and not preceded by fever or any other illness. Direct laryngoscopy confirms the diagnosis.

3. Laryngospasm: It may occur in patients with *hypocalcemic tetany* but it is usually associated with corpopedal spasm. Diagnosis depends on the presence of hypocalcemia and a dramatic response to I.V. calcium gluconate. The attack is usually short but it may recur several times per day.

4. Laryngeal edema: It may occur with *severe allergy* as angioneurotic edema or serum sickness. It may also follow extubation of endotracheal tube especially with prolonged intubation *(post-extubation stridor).*

5. Laryngeal compression: Acute laryngeal compression and stridor may occur with traumatic retropharyngeal hematoma or with retropharyngeal abscess. The possibility of retropharyngeal abscess should be considered in patients presenting with high fever, stridor and difficult swallowing. Characteristic features include drooling of secretions from the mouth due to difficult swallowing, hyperextension of the neck, and

a bulge on the posterior pharyngeal wall. The diagnosis can be confirmed by a lateral x-ray of the nasopharynx or the neck, which reveals a retropharyngeal mass. CT scan is more sensitive.

Causes of high fever and stridor

Acute epiglottitis: Rapid progression. Swollen epiglottis.
Acute tracheitis: Slow progression. Normal epiglottis.
Retropharyngeal abscess: Slow progression. Bulge on posterior pharyngeal wall.

B) CHRONIC STRIDOR

Chronic stridor can be congenital (present since birth) or acquired and can be caused by laryngeal or tracheal causes.

1. Congenital chronic stridor: ***Laryngomalacia*** (due to flabbiness of epiglottis and subglottic aperture) is the most common cause. Stridor is only mild and becomes more evident with crying or when the infant lies on his back. The condition gradually subsides over several months or by the end of the first year. Direct laryngoscopy is important for diagnosis and for exclusion of ***other laryngeal causes*** especially laryngeal web, laryngeal tumors or laryngeal cysts. ***Congenital laryngeal compression*** as in hypoplasia of the mandible, macroglossia, congenital goiter or vascular rings should be also considered. ***Birth trauma to larynx***, although not congenital, should be considered in the early onset stridor. It may lead to dislocation of cricothyroid articulation or cord paralysis.

2. Acquired chronic stridor: ***Chronic laryngeal stenosis*** following prolonged intubation or high tracheostomy is the commonest cause. ***Subglottic tracheal stenosis*** may also occur due to similar causes. ***Laryngeal tumors*** should be also considered especially when hoarseness of voice is the initial symptom. Benign papilloma is the most common tumor in children. ***Laryngeal paralysis*** due to recurrent laryngeal nerve injury or bulbar paralysis may be also responsible. ***Laryngeal compression*** by a retro-pharyngeal mass or thyroid enlargement may be occasionally the cause.

4. Wheezing

Acute wheezing	Recurrent and chronic wheezing
Acute bronchiolitis	Bronchial asthma
Acute bacterial bronchopneumonia	Foreign body inhalation
Transient bronchial hyperreactivity	Recurrent aspiration
Foreign body inhalation	Chronic infections
Acute congestive heart failure	Bronchopulmonary dysplasia
Organic phosphate poisoning	Bronchiolitis obliterans
+	Airway compression
? First episode of asthma	Recurrent or chronic heart failure

Expiratory wheezing is one of the most common presentations in pediatric practice. It is a continuous expiratory musical sound produced by partial obstruction, localized or generalized, at the level of small bronchi and bronchioles (lower airway obstruction).

- What is the degree of lower airway obstruction?
- What is the cause?

1. *What is the degree of lower airway obstruction?*

Clinical assessment of the degree of lower airway obstruction is very important for the decision regarding the place and line of management.

Clinical grading of wheezing

Grade I (Wheezing only)
Prolonged expiration and expiratory wheezing are the only findings.
No respiratory distress or diminished air entry.

Grade II (Wheezing and tachypnea)
Prolonged expiration and expiratory wheezing.
Rapid respiration (tachypnea) and slightly diminished air entry.

Grade III (Wheezing and retractions)
Prolonged expiration and expiratory wheezing.
Rapid respiration, retractions (intercostal, suprasternal) and moderately diminished air entry.

Grade IV (Wheezing and cyanosis)
Rapid respiration, marked retractions and cyanosis.
Markedly diminished air entry.
Wheezing is minimal or even absent, "silent chest" or "tight chest".

- Infants and children with wheezing and respiratory distress should be hospitalized.

2. What is the cause?

A) ACUTE WHEEZING

Wheezing for the first time (acute wheezing) should suggest the following

1. Acute bronchiolitis: It is a common interstitial pneumonia that causes inflammatory obstruction of the small airways. It mainly occurs in ***infants*** with a peak incidence around the age of 6 months (3 months - 2 years). The illness is viral in origin. Respiratory syncytial virus is the main organism but other viruses as adenovirus or parainfluenza viruses may be causative agent. Mycoplasma infection is occasionally the responsible agent. A history of contact to older children or adults with mild respiratory illness is usually obtained.

- The course of illness runs through ***3 stages***, each for few days:

a) Nasopharyngitis and fever: The illness starts with mild to moderate fever (38.0 - 39.5°C) and nasal discharge for few days.

b) Respiratory distress and wheezing: The infant rapidly develops the features of respiratory distress with rapid respiration (respiratory rate is 60-80/minute) and retractions. Cough is present and may be prominent. Chest auscultation reveals expiratory wheezing. Fine crepitations at the end of inspiration and beginning of expiration may be heard and air entry may be diminished in severe cases. Areas of bronchial breathing due to segmental collapse can be heard in 30% of cases. This stage usually lasts for few days but prolonged course may occur with adenovirus infection.

c) Rapid improvement: Within few days, manifestations of respiratory distress and wheezing disappear but cough may remain for another week.

- The most serious complications are respiratory failure and dehydration, so, hospitalization, oxygen therapy and I.V. fluids are important.

- Prognosis is generally good. Mortality rate does not exceed 1% and is mostly related to adenovirus infection. It is important to remember that the illness, on the other extreme, can be mild and presenting only with mild wheezing and without distress.

- Chest x-ray reveals a hyperinflated chest (generalized obstructive emphysema). Areas of segmental collapse may be also present. Chest x-ray is also useful to differentiate the condition from bacterial bronchopneumonia. CBC and CRP are also useful for differentiation in doubtful cases.

- In one third of cases, a second or even a third attack may occur later. In this group, the possibility of developing bronchial hyperreactivity and asthma is considerable especially in those with positive family history.

2. Severe bacterial bronchopneumonia: When bacterial bronchopneumonia is associated with significant obstruction, generalized obstructive emphysema and expiratory wheezing occur. Clinically, fever is usually high (above 39.5°C) and fine inspiratory crepitations are more evident than wheezing. CBC (polymorphonuclear leukocytosis) and CRP (raised) are useful for differentiation from bronchiolitis.

3. Viral-induced transient bronchial hyperreactivity: With viral respiratory infections as viral bronchitis or viral interstitial pneumonias, transient bronchial hyperreactivity may occur and leads to bronchospasm and expiratory wheezing. The possibility should be considered when bronchitis is associated with expiratory wheezing especially in children above 2 years when diagnosis of bronchiolitis is unlikely and history of previous attacks of wheezing is lacking. The condition should be also considered in children with viral interstitial pneumonia and expiratory wheezing.

4. Foreign body inhalation: The possibility should be considered in every case of acute wheezing especially when the onset is sudden, associated with choking and not preceded by any illness. The possibility becomes greater when wheezing is intractable and not responding to bronchodilator therapy. Diagnosis is confirmed by brochoscopy.

5. Acute congestive heart failure: In addition the wheezing which may be present, the clinical triad of disproportionate tachycardia, tachypnea and enlarged tender liver is well evident (see congestive heart failure).

6. Organic phosphorus poisoning: This serious insecticide poisoning should be considered in patients presenting with respiratory distress, profuse bronchial secretions, bronchospasm and wheezing. Associated lacrimation, salivation, disturbed consciousness and miosis (or pinpoint pupils) make the possibility great. When poisoning occurs through inhalation, respiratory manifestations appear first and are prominent. With poisoning through ingestion, vomiting and diarrhea occur first and the odor of garlic on the breath can be prominent.

7. First episode of asthma: Although there is always a first episode of wheezing, diagnosis of bronchial asthma should never be made on the basis of a single wheezing episode. Even in patients with positive family history of asthma, the diagnosis is only considered if wheezing recurs.

B) RECURRENT AND CHRONIC WHEEZING

1. Bronchial asthma: It is by far the most common cause of recurrent and chronic wheezing in children. Although it mainly occurs in children above 2 years, it may also occur in infants. However, wheezing in infancy should stimulate the search for other causes. Diagnosis is mainly clinical and depends on the suggestive clinical manifestations and exclusion of other causes of wheezing. Confirmatory evidences include positive family history, challenge tests and the therapeutic response to bronchodilators (see below).

2. Foreign body inhalation: It should be considered when the onset of the initial episode was sudden, associated with choking and not preceded by any illness. Intractable wheezing not responding to bronchodilators should also suggest the diagnosis. Even in known asthmatic children, an acute episode of wheezing not responding to bronchodilators may also suggest a foreign body inhalation (asthmatic children, as other children, are also subjected to foreign body inhalation).

3. Recurrent aspiration: Recurrent or persistent wheezing in early infancy should always raise the possibility. Gastroesophageal reflex, tracheoesophageal fistula and cricopharyngeal incoordination are the main causes. Barium swallow under screen can differentiate between these conditions.

4. Chronic infections: Chronic infection in cystic fibrosis is an important cause of wheezing in infants or children. Positive family history of other affected siblings should raise suspicion. Bronchiectasis should be also considered.

5. Bronchopulmonary dysplasia: It is an important cause of chronic cough, chronic respiratory distress and chronic wheezing. The illness mostly occurs in neonates and young infants who were subjected to prolonged mechanical ventilation.

6. Bronchiolitis obliterans: It is a serious complication of several infectious agents especially adenovirus, mycoplasma and pertussis. It is characterized by chronic cough, chronic or persistent respiratory distress and chronic wheezing. The possibility should be considered in patients with acute bronchiolitis when the course is extending over weeks without an apparent improvement. Chest x-ray reveals pulmonary infiltrate. Corticosteroids may be useful in some cases.

7. Airway compression: Chronic wheezing especially when localized and not associated with respiratory distress should raise the possibility of airway compression. Vascular rings, lung cyst, enlarged nodes or tumours should be considered.

8. Recurrent or chronic congestive heart failure: It should be remembered that wheezing could be also caused by cardiac conditions. Exertional dyspnea and manifestations of systemic congestion are the main presentation (see heart failure).

Diagnosis of childhood asthma

Bronchial asthma is the most common chronic illness in children. It is estimated that at least 10% of children experience episodic (paroxysmal) wheezing.

- ***Chronic bronchial hyperresponsiveness:*** The basic factor in pathogenesis of asthma is the chronic bronchial hyperreactivity or hyperresponsiveness (i.e., the bronchial system in asthmatic patients is "oversensitive" or "twitchy" and can be easily stimulated). The degree of hyperreactivity is constant in the same patient and is proportionate to the degree of severity of asthma.

- ***Asthma triggers:*** The acute asthmatic attack occurs when the hyperreactive or hyperesponsive airway is exposed to a triggering factor (asthma triggers) as viral infection, allergy or exercise. These factors induce the release of *asthmogenic chemical mediators* from mast cells and other cells as neutrophils and platelets.

- ***Airway obstruction, inflammation and remodeling:*** The chemical mediators (as histamine, leukotrienes, prostaglandins) will induce bronchoconstriction and mucosal inflammation. Stuctural changes in the airways (airway remodeling) occur in long-standing and severe inflammation. These changes include basement membrane thickening, subepithelial collagen deposition and hypertrophy of smooth muscles and hyperplasia of mucus glands.

- How to diagnose asthma?
- What is the severity of the acute attack?
- What is the cause of the acute attack?
- What is the type of asthma?

1. How to diagnose asthma?

Bronchial asthma has 2 main clinical presentations:

1. Recurrent or episodic wheezing: Most patients with childhood asthma present clinically with recurrent attacks of wheezy chest. However, diagnosis of asthma is only made after exclusion of other causes of recurrent wheezing. It is very important to emphasize that diagnosis of asthma should never be made on the basis of a single wheezing episode. Confirmatory evidences for diagnosis include positive family history, eosinophilia and therapeutic response to bronchodilators.

2. Chronic night cough: Some asthmatic patients present clinically with the complaint of chronic night cough without an evident or documented wheezing. In these patients, exclusion of other causes of chronic night cough especially chronic sinusitis is important. In case of suspicion, therapeutic response to bronchodilators and asthma controllers is an indirect evidence for diagnosis (see chronic cough).

In the great majority of patients with bronchial asthma, ***diagnosis is entirely made on clinical basis***. However, in some patients especially when the diagnosis is uncertain, or the patient is not properly controlled, laboratory diagnosis becomes necessary.

Laboratory diagnosis of bronchial asthma

Chest x-ray
Generalized obstructive emphysema during the acute attack and in chronic longstanding cases.

Challenge tests (to prove bronchial hyperresponsiveness)
Nonspecific bronchial challenge tests: Response to exercise or inhalation of mist.
Specific bronchial challenge tests: Response to specific allergens.

Skin tests and IgE (to prove allergy in allergic cases)
Skin tests: It is a simple and quick test to detect allergy to a broad spectrum of allergens.
Total serum IgE and allergen-specific IgE.

Evaulation of pulmonary function (to detect lower airway obstruction)
By peak expiratory flow device (Peak flow meter): Decreased peak expiratory flow (PEF).
It is a simple device that can be used in clinics and at home.
By spirometry: Decreased forced expiratory flow (FEV) and forced vital capacity (FVC).

- **Peak expiratory flow (PEF)** is made twice daily (morning and evening) over one month.

Normal PEF in children is about 220 Liter/minute. Results can be classified as:
- Green zone: 175-220 Liter/minute. (80-100% of expected).
- Yellow zone: 110-175 Liter/minute. (50-80% of expected).
- Red zone : Less than 110 Liter/minute. (less than 50% of expected).

2. *What is the severity of the acute attack?*

Clinical assessment of the severity of the acute attack (asthma exacerbation) is very important for the clinical decision regarding the place and line of management.

Clinical grading of acute asthmatic attack

Grade I: Mild acute asthma (Wheezing only)
Prolonged expiration and expiratory wheezing are the only findings.
No respiratory distress or diminished air entry.
These patients can be safely managed at home.

Grade II: Moderate acute asthma (Wheezing and tachypnea)
Prolonged expiration and expiratory wheezing.
Rapid respiration (tachypnea) and slightly diminished air entry.
These patients can be managed at home but preferably in hospital.

Grade III: Severe acute asthma (Wheezing and retractions)
Prolonged expiration and expiratory wheezing.
Rapid respiration, retractions (intercostal, suprasternal) and moderately diminished air entry.
These patients should be hospitalized, preferably in an intensive care unit.

Grade IV: Profound acute asthma (Wheezing and cyanosis)
Rapid respiration, marked retractions and cyanosis.
Markedly diminished air entry.
Wheezing is minimal or even absent. "Silent chest" or "tight chest".
These patients should be immediately admitted to an intensive care unit.

- Clinical assessment in hospitalized children should be combined with measurement of arterial oxygen saturation and blood gas analysis for proper assessment of ventilatory functions.

3. *What is the cause of the acute attack?*

Bronchial asthma is not a single disease. The triggering stimuli that precipitate the acute attack *(asthma triggers)* are different from patient to patient. Even in the same patient, acute attacks may be precipitated by more than one stimulus. According to these triggers or stimuli, asthma is classified as:

1. Viral-induced asthma: Viral respiratory infections as common cold or bronchitis are the triggering precipitating factor in 40% of cases. The mechanism of mediator release is not through IgE. Pure viral-induced asthma is much commoner in *infants and young children* and terms as "Wheezy bronchitis", "asthmatic bronchitis' or "wheezy infant" are commonly used. The *prognosis* for ultimate cure is good, as 70% of cases will remit completely in late childhood while 30% may turn to allergic asthma.

2. Allergic asthma: Respiratory allergy is the triggering precipitating factor in 50% of cases. The mechanism of mediator release is through IgE. The acute attacks are precipitated by exposure to *pneumoallergens* (as house dust, mites, pollen or fur) or less commonly to *alimentary allergens* (as eggs, fish, banana or chocolate). *Viral respiratory infections* may also precipitate the acute attacks. The condition is much commoner in children and prognosis for ultimate cure is less favorable than viral-induced asthma.

3. Exercise-induced asthma: Severe physical exercise can induce an acute attack in 30% of cases. The mechanism of mediator release is through airway cooling. It is characterized by moderate bronchospam during exercise and severe bronchospasm after return to resting condition.

Other factors may be also responsible in some patients. ***Environmental factors*** (humidity, cold air, cigarette smoke or car exhaust fumes) and ***emotional factors*** (stress, anger or frustration) may aggravate the condition is some patients. ***Drugs*** as aspirin (aspirin-induced asthma) may be responsible.

4. *What is the type of asthma?*

Bronchial asthma is a chronic disease. With long term follow up and according to *frequency and severity* of symptoms, asthma can be classified as:

1. Intermittent asthma: It is the commonest type. There are no symptoms between the acute attacks where the chest is completely free. It can be classified as *infrequent* intermittent asthma (attacks recur every several weeks or months) and *frequent* intermittent asthma (attacks recur every few weeks). It can be also classified according to severity of attacks as *mild, moderate* and *severe*. Severe intermittent asthma is characterized by recurrent severe attacks and frequent hospitalization.

2. Seasonal asthma: Some allergic patients only develop symptoms in a certain season (allergy to pollens in April to June and allergy to mites in August to September).

3. Persistent asthma: It is the severest form of asthma. It is characterized by persistent symptoms (cough and expectoration) between the acute attacks. According to the severity of symptoms it can be also classified as mild, moderate and severe persistent asthma. Patients with persistent asthma are in need of asthma controller medications (See below and see Practical Pediatric Therapy).

Clinical grading of persistent asthma (By NAEPP)

Mild persistent asthma
Days with symptoms are more than 3 days per week.
Night symptoms are more than 3 nights per month.

Moderate persistent asthma
Daily symptoms with daily use of beta agonists.
Night symptoms are more than once per week.

Severe persistent asthma
Daily symptoms with limited physical activity and frequent exacerbations.
Night symptoms are frequent.

- **NAEPP** (National Asthma Education and Prevention Program).
- The " **3 strikes rule**" is an easy rule to identify asthmatic children who are in need of asthma controller medications. The asthmatic child is in need of controller therapy if he has any of the following 3 criteria: 1. If he has asthma symptoms more than 3 times per week.
  2. If he has night symptoms more than 3 times per month.
  3. If he needs to use more than 3 containers of relief inhalers per year.

5. Respiratory Distress

Pulmonary causes	Extrapulmonary causes
Common causes	**Acute congestive heart failure**
Pneumonias	Acute myocarditis (contractility failure)
Acute bronchiolitis	Infective endocarditis
Acute asthmatic attack	Myocardial ischemia (shock, hypoxia)
Aspiration syndromes	Acute arrhythmias
Pulmonary edema	Acute hypervolemia (preload failure)
Adult respiratory distress syndrome	Acute hypertension (afterload failure)
Other causes	**Acute metabolic acidosis**
Pleural effusion	Shock, severe hypoxia, sepsis
Pneumothorax	Gastroenteritis and dehydration
Obstructive emphysema	Acute renal failure
Massive lung collapse	Diabetic ketoacidosis
Organic phosphate poisoning	Salicylate poisoning
Bronchopulmonary dysplasia	Acute on top of chronic
Bronchiolitis obliterans	**Acute severe anemia**
Respiratory paralysis	Severe blood loss or hemolysis

Severe stridor is also associated with respiratory distress (see stridor)

Respiratory distress is the most common emergency in infancy and childhood and the most common cause of hospital admissions. Pneumonias, acute bronchiolitis and acute asthmatic attack are by far the most common causes.

- What is the degree of distress?
- What is the cause of distress?

1. *What is the degree of distress?*

Clinical assessment of the degree of distress is important for determination of the severity and course of illness and for choice of the appropriate line of respiratory support.

Clinical grading of respiratory distress

Grade I (mild distress): Rapid respiration (tachypnea) and working alae nasi.
Grade II (moderate distress): Intercostal and subcostal retractions.
Grade III (severe distress): Expiratory grunting.
Grade IV (advanced distress): Central cyanosis and disturbed consciousness.

Important remarks

1. **Rapid respiration** is the first compensatory mechanism of the body to improve oxygenation and ventilation.
2. **Retractions** are more marked with obstructive airway disease. With severe obstruction, suprasternal retractions also occur. Retractions are caused by forceful contractions of intercostal muscles and diaphragm to improve ventilation through increasing the tidal volume.
3. **Grunting** is mainly evident in neonates and infants with severe alveolar disease and it may be absent in obstructive airway disease. It is the last compensatory mechanism of the body to improve oxygenation. It aims to increase intra-alveolar pressure (physiological PEEP).
4. **Cyanosis** appears after failure of all compensatory mechanisms and it indicates a frank respiratory failure with PaO_2 below 35 mmHg. ***Altered consciousness*** occurs due to severe hypoxemia and/or marked CO_2 retention (CO_2 narcosis occurs with $PaCO_2$ above 60 mmHg).
5. **Laboratory confirmation:** Clinical assessment should be combined with:
   * ***Arterial oxygen saturation*** by pulse oximeter (Normal saturation is above 95%).
   * ***Blood gas analysis*** to detect acidosis and respiratory failure (PaO_2 below 50 mm Hg with or without $PaCO_2$ above 60 mm Hg).

Types of respiratory failure

	Lung failure	Pump failure
Other names	Type I respiratory failure Peripheral respiratory failure	Type II respiratory failure Central respiratory failure
Basic defect	Poor arterial oxygenation	Alveolar hypoventilation
Causes	Causes of respiratory distress • Pulmonary causes • Extrapulmonary causes	Respiratory pump failure • Respiratory depression (deep coma) • Respiratory paralysis • Respiratory fatigue (severe lung failure)
Clinically	Respiratory distress Chest signs	Shallow breathing, cyanosis Coma or paralysis
Blood gases	Arterial hypoxemia (low PaO_2) ± hypoventilation (high $PaCO_2$) Acute respiratory acidosis	Hypoventilation (high $PaCO_2$) ± arterial hypoxemia (low PaO_2) Acute respiratory acidosis
Therapy	Oxygen therapy ± assisted ventilation	Assisted ventilation ± oxygen therapy

- With central respiratory failure due to respiratory depression, coma is the main presentation and respiration is shallow, slow and may be irregular (see coma).
- With central respiratory failure due to respiratory paralysis, acute paralysis (bulbar and limb paralysis) is the main presentation and respiration is shallow and rapid.

2. *What is the cause of distress?*

In spite of the long list of conditions presenting with respiratory distress, it is usually not difficult to distinguish between the different causes based on the history, examination and simple investigations.

Diagnostic approach of respiratory distress

History

- History suggesting pneumonia (Fever, preceding upper respiratory infection).
- History of previous similar attacks: Bronchial asthma, diabetic ketoacidosis.
- History of aspiration during feeding or aspiration of foreign body.
- History of accidental poisoning: Organic phosphorus or salicylates.
- History suggesting renal disease: Acute renal failure.

Examination

- Intense pallor: Severe anemia.
- Deep rapid respiration with altered consciousness: severe metabolic acidosis.
- Tachycardia, tachypnea and tender liver: Acute congestive heart failure.
- Chest signs
  - Unilateral diminished air entry: Effusion, pneumothorax, emphysema, collapse.
  - Fine consonating crepitations: Bronchopneumonia, bronchiolitis, ARDS.
  - Course crepitations (drowned chest): Aspiration, pulmonary edema, organic phosphorus.
  - Expiratory wheezing: Bronchiolitis, asthma, foreign body, heart failure.
  - Lobar bronchial breathing: Lobar pneumonia, lobar collapse.
- Systemic examination
  - Hypertension, arrhythmias or cardiac murmurs: Acute congestive heart failure.
  - Bulbar paralysis or limb paralysis: Respiratory paralysis.
  - Severe diarrhea and dehydration: Metabolic acidosis, ARDS.

Investigations

- Chest x-ray (In ALL cases): To distinguish between different pulmonary causes.
- Blood gases (In ALL cases): To detect metabolic acidosis and respiratory failure.
- Sepsis screen (CBC, ESR, CAP): With suspected pneumonia.
- Renal function (Blood urea, creatinine): With suspected acute renal failure.
- Blood sugar level: With suspected diabetic ketoacidosis.
- Echocardiography: With suspected cardiac disease.

A) PULMONARY CAUSES

1. Pneumonia: It is the commonest cause of respiratory distress in infants and young children. Fever and preceding rhinitis are important associated findings. Diagnosis should include the pathological type (lobar, bronchopneumonia, interstitial pneumonia), the cause (bacterial, viral or other agents) and the associated complications (see below).

2. Acute bronchiolitis: It is a common cause of respiratory distress and expiratory wheezing in infants. Clinical differentiation from other causes of acute wheezing is important (see acute wheezing).

3. Acute asthmatic attack: Bronchial asthma is the commonest cause of recurrent respiratory distress and wheezing in children. Clinical differentiation from other causes of recurrent wheezing is important. Diagnosis should include the severity of the acute attack, cause of the acute attack as well as the type of asthma (see recurrent wheezing and diagnosis of asthma).

4. Aspiration syndromes: The possibility of aspiration should be always considered when the onset is sudden and not preceded by any illness. ***Foreign body inhalation*** is an important cause of respiratory distress and wheezing not responding to bronchodilators. ***Aspiration of foods or medicines*** is an important cause of sudden distress, which may lead to aspiration pneumonia or even to cardiopulmonary arrest. Chest examination usually reveals coarse bubbling crepitations. ***Recurrent aspiration*** should suggest gastroesophageal reflux, tracheoesophageal fistula or cricopharyngeal incoordination. ***Near-drowning*** (water aspiration) is occasionally the cause. Aspiration should not be confused with other causes of coarse bubbling crepitations especially pulmonary edema and organic phosphorus poisoning.

5. Pulmonary edema: it is a serious condition characterized by transudation of fluids from pulmonary capillaries into the interstitial spaces and alveoli. The illness results from both ***cardiac*** (increased capillary pressure) and ***noncardiac*** (increased capillary permeability or increased negative interstitial pressure) causes. Clinically, respiratory distress and coarse bubbling crepitations are the main findings. Chest x-ray reveals a hazy to opaque infiltrate, which may be more on one side (see Basic Pediatric Radiology). Clinical evaluation should be also directed to identify the causative disease.

Causes of pulmonary edema

Increased pulmonary capillary pressure (Cardiogenic pulmonary edema)

- Severe acute congestive heart failure (especially severe myocarditis)
- Postoperative period of open-heart surgery

Increased pulmonary capillary permeability

- Severe pneumonia (fulminant bacterial or viral interstitial pneumonia).
- Aspiration pneumonia and near-drowning
- Inhalation pneumonia (toxic gases as ammonia, NO_2 or high oxygen concentration).
- Adult respiratory distress syndrome (ARDS).
- Severe septic shock with endotoxemia (diffuse capillary leak syndrome).
- Anaphylaxis with release of vasoactive substances as histamine or leukotrienes.
- Renal diseases (glomerulonephritis, acute and chronic renal failure).
- Iatrogenic fluid overload (from too rapid or too large intravenous fluids).

Increased negative interstitial pressure

- Severe upper airway obstruction (as epiglottitis) causing negative interstitial pressure.
- Rapid expansion of collapsed lung with pneumothorax (reexpansion pulmonary edema).

Other causes

- Neurogenic pulmonary edema: With increased intracranial pressure or severe head injury.
- High altitude pulmonary edema.

6. Adult respiratory distress syndrome (ARDS): It is a catastrophic lung disease characterized by a diffuse alveolar-capillary membrane injury, which results in impairment of oxygenation and development of interstitial and alveolar pulmonary edema. Shock (especially septic shock) is the most important cause and hence the disease is also known as ***"shock lung"***. Other less frequent causes include DIC, drug overdosage, toxic gas inhalation and aspiration. The mechanism of capillary injury is through the release of potent mediators from endotoxins, several cells (including neutrophils, macrophages, eosinophils) and platelets. These mediators include oxygen free radicals, proteolytic enzymes, arachidonic acid metabolites, platelet activating factor and fibrin degradation products. The condition should be suspected in any critically sick patient who develops respiratory distress. Severe gastroenteritis and dehydration is a good example. Respiratory distress usually appears within 2 days of the lung injury and it is usually severe, accompanied with cyanosis and resistant to simple oxygen therapy. Chest auscultation is initially free but fine bilateral crepitations soon appear. Chest x-ray reveals fine reticular or reticulonodular infiltrate. With frank pulmonary edema, hazy to opaque infiltrate appears. Prognosis is bad and prolonged mechanical ventilation is always necessary and can be life-saving.

7. Pleural effusion: Bacterial pneumonias are by far the most common cause of pleural effusion and empyema in infants and young children. The illness should be suspected in any case of respiratory distress with markedly diminished air entry over one side. Stony dullness over the involved side and mediastinal shift to the other side are usually evident. Urgent chest x-ray reveals a dense opacity occupying one hemithorax with mediastinal shift to the other side (see Basic Pediatric Radiology).

8. Pneumothorax: Beyond the neonatal period, isolated pneumothorax (without fluid) is uncommon and is mainly caused by mechanical ventilation, chest surgery, chest trauma, severe bronchiolitis, severe pertussis and severe interstitial pneumonia. In addition to respiratory distress, markedly diminished air entry and hyperresonance over the involved side are evident with mediastinal shift to the other side. Urgent chest x-ray reveals hypertransradiant hemithorax with absent bronchovascular markings and mediastinal shift to the other side. Hydropneumothorax is probably commoner than pneumothorax (see Basic Pediatric Radiology).

9. Localized obstructive emphysema: Obstructive emphysema of a whole lung results from incomplete obstruction of the right or left main stem bronchus mostly by a foreign body of viscid secretions. Clinically, respiratory distress and diminished air entry over the affected side are the main findings. Chest x-ray reveals hypertransradiant hemithorax with preserved bronchovascular markings and some mediastinal shift to the other side (see Basic Pediatric Radiology).

10. Massive lung collapse: Massive collapse of one lung results from complete obstruction of its main stem bronchus mostly by foreign body. It may also occur following chest surgery or in intubated patients if the tube is advanced in one main stem bronchus (usually the right), which leads to complete obstruction of airflow and collapse of the other lung (usually the left). Clinically, respiratory distress, diminished air entry and bronchial breathing over the affected side are the main findings. Chest x-ray reveals opaque hemithorax with mediastinal shift to the same side of the lesion.

11. Organic phosphorus poisoning: This serious insecticide poisoning should be considered in patients presenting with respiratory distress, profuse chest secretions and may be bronchospasm and wheezing. Associated lacrimation, salivation, disturbed consciousness and miosis (or pinpoint pupils) make the possibility great. The condition should be differentiated from other causes of respiratory distress with coarse bubbling crepitations especially aspiration and pulmonary edema (see also wheezing).

12. Bronchopulmonary dysplasia: It is an important cause of chronic cough, chronic or persistent respiratory distress and chronic wheezing. The illness mostly occurs in neonates and young infants who were subjected to prolonged mechanical ventilation (see neonatal respiratory distress).

13. Bronchiolitis obliterans: It is a serious complication of several infectious agents especially adenovirus, mycoplasma and pertussis. It is characterized by chronic cough, chronic or persistent respiratory distress and chronic wheezing. The condition should be suspected in patients with acute bronchiolitis when the course is extending over weeks without an apparent improvement. Chest x-ray reveals a pulmonary infiltrate (miliary, reticulonodular or parahilar peribronchial).

14. Respiratory paralysis: With ***acute paralysis*** of respiratory muscles, the respiration becomes shallow and rapid. Clinically, bulbar paralysis and limb paralysis are the main presentation. The condition results in alveolar hypoventilation with CO_2 retention (pump failure or central respiratory failure). Guillain-Barre syndrome is the most common cause. Diphtheria, botulism and poliomyelitis are other causes. In severe cases, prolonged mechanical ventilation is lifesaving. ***Gradual chronic*** respiratory paralysis occurs with Werdnig-Hoffmann disease, muscular dystrophies and myasthenia gravis.

Causes of persistent or chronic respiratory distress

Slowly resolving pneumonia (inadequate therapy, immunodeficiency, obstructive bronchial lesions).
Adult respiratory distress syndrome (ARDS).
Persistent emphysema or collapse.
Bronchopulmonary dysplasia.
Bronchiolitis obliterans.
Respiratory paralysis.

B) EXTRAPULMONARY CAUSES

1. Acute congestive heart failure: Clinical diagnosis depends on the presence of the cardinal triad of 3 T (tachycardia, tachypnea and enlarged tender liver). In severe cases, pulmonary edema and/or cardiogenic shock occur (see congestive heart failure).

2. Acute metabolic acidosis: The possibility of metabolic acidosis should be always in mind in every case of respiratory distress. Clinical diagnosis depends on the presence of deep rapid respiration (Kussmaul or acidotic breathing). In severe cases,

disturbed consciousness becomes evident. Clinical suspicion should be confirmed by blood gas analysis where all parameters are low (pH, bicarbonate and $PaCO_2$). The severity of acidosis can be determined by the degree of lowering of pH and bicarbonate level.

Normal blood gases

pH	7.35 - 7.4
Bicarbonate	20 - 24 mEg/litre
$PaCO_2$	35 - 40 mmHg
PaO_2	90 - 100 mmHg
For assessment of acid-base status venous samples are satisfactory	

Grades of metabolic acidosis

	pH	Bicarbonate
Mild	Below 7.3	Below 16 mEq/liter
Moderate	Below 7.2	Below 13 mEq/liter
Severe	Below 7.1	Below 10 mEq/liter
Profound	Below 7.0	Below 7 mEq/liter

The cause of acidosis can be identified by both clinical and laboratory evaluation. Gastroenteritis and dehydration, acute renal failure and diabetic ketoacidosis are the most common. In critically sick patients, shock, hypoxia and sepsis should be also considered. In patients with respiratory failure, picture of "mixed metabolic and respiratory acidosis" occurs where the pH is markedly decreased while bicarbonate and $PaCO_2$ are near normal values. Acute metabolic acidosis may also occur on top of chronic acidosis. The main causes of chronic acidosis are aminoacidopathies, disorders of carbohydrate metabolism (glycogenosis type I and disorders of intermediary carbohydrate metabolism), renal tubular acidosis and chronic renal failure (see genetic disorders). Metabolic acidosis should not be confused with other acid-base disturbances whether isolated or mixed.

Disorders of acid-base balance

	Metabolic acidosis	Respiratory acidosis	Metabolic alkalosis	Respiratory alkalosis
pH	Low	Low	High	High
Bicarbonate	Low	High	High	Low
$PaCO_2$	Low	High	High	Low

3. Acute severe anemia: Massive hemorrhage or severe hemolytic crisis is commonly associated with rapid respiration due to severe hypoxia. Intense pallor and altered consciousness (hypoxic anemic encephalopathy) are the main findings. With acute hemolytic anemia, dark urine and mild jaundice may be also present (see anemia).

Diagnosis of pneumonias

Pneumonia is a common and serious lower respiratory infection characterized by inflammation and consolidation of the alveoli, interstitial tissues or both (i.e. inflammation of the parts responsible for gas exchange).

Pneumonia should be considered in every case of acute cough and respiratory distress especially when it is associated with fever. Diagnosis should include the pathological type, the cause and the associated complications.

- What is the pathological type?
- What is the causative agent?
- What are the associated complications?

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1. *What is the pathological type?*

The diagnostic clinical signs of pneumonia vary according to the pathological type:

1. Lobar pneumonia: It is characterized by the following:

- It is usually *unilateral* and the infection is limited to one lobe. In many cases, more than one lobe on the same side may be involved and the term "right sided" or "left sided" pneumonia can be used according to the involved side. In some cases, the infection is lobular or patchy and the term "lobular or patchy" pneumonia can be used. Pleural effusion (minimal, moderate or massive) is a common complication.
- The main auscultatory findings are *bronchial breathing and increased vocal resonance* over the area corresponding to the involved lobe or lobes. Fine crepitations may be heard and some dullness is usually present.
- Lobar pneumonias are mostly *bacterial* in origin. Pneumococcal pneumonia is the commonest cause but in children under 2-3 years, hemophilus influenza is more common. Other bacterial agents as staphylococci, streptococci and klebsiella come next. Mycoplasma pneumonia should be also considered in school age children especially when the illness is accompanied with spasmodic cough and not associated with respiratory distress. Tuberculosis may be also considered in certain situations.
- Chest x-ray reveals a picture of lobar consolidation (see Basic Pediatric Radiology).

2. Bronchopneumonia: it is characterized by the following:

- It is usually *bilateral* and the infection is in the form of small patches of consolidation along the distribution of the bronchial tree. The lower lobes are usually more affected so examination of the back is more important.
- The main auscultatory finding is *bilateral fine consonating crepitations* mainly over the lower lobes. In severe cases with significant lower airway obstruction, generalized obstructive emphysema and expiratory wheezing may occur. In these cases, differentiation between bacterial bronchopneumonia and viral bronchiolitis is important (see acute wheezing).
- Bronchopneumonia is *bacterial or viral*. Bacterial bronchopneumonia is more serious and is usually associated with high fever, toxic look and marked respiratory distress. With viral bronchopneumonia, the patient does not look sick and chest signs are more than the degree of distress.

• Chest x-ray reveals patchy or fluffy cotton infiltrate (in bacterial cases) or fine reticulonodular infiltrate in viral cases (see Basic Pediatric Radiology).

3. Interstitial pneumonia: It is characterized by the following:

• It is usually *bilateral* and the infection is in the form of small foci of consolidation along the distribution of the small bronchioles (bronchiolar pneumonia).

• Clinically, interstitial pneumonia has *4 main characteristics*: (1) Severe spasmodic cough (uncommon with lobar and bronchopneumonia), (2) significant respiratory distress with minimal chest signs, (3) tendency to prolonged expiration and expiratory wheezing and (4) prolonged course over several weeks.

• Interstitial pneumonias are mostly *viral*. Respiratory syncytial virus, parainfluenza viruses, adenovirus, rhinovirus and influenza virus are the main causative agents. Insterstitial pneumonia can be also caused by other agents especially pneumocystis carinii pneumonia (interstitial plasma cell pneumonia).

• Chest x-ray reveals a parahilar peribronchial pulmonary infiltrate or reticulonodular infiltrate (see Basic Pediatric Radiology).

2. What is the causative agent?

Most cases of pneumonia are bacterial or viral. Other etiological agents as mycoplasma, pneumocystis carinii and fungi should be also considered. Although accurate differentiation cannot be made except with isolation of the causative agent, history, clinical examination and simple investigations are very useful in suggesting the causative agent. The most important clinical problem is the differentiation between bacterial and viral pneumonia.

1. Bacterial pneumonia: It is usually lobar or bronchopneumonia. The possibility should be considered when the fever is high and the patient looks seriously sick. The course is usually severe and complications are common. Simple investigations (CBC, CRP, ESR) and chest x-ray are useful for confirmation and for differentiation from viral pneumonias. The causative agents can be also suggested:

a) Pneumococcal pneumonia: It is by far the most common type (90% of bacterial pneumonias). It is usually bronchopneumonia below 4 years and lobar pneumonia above 4 years. Complications can occur but prognosis is generally good and mortality is unusual.

b) Staphylococal pneumonia: It is the most serious and the most fulminant pneumonia. It is commoner in infants (70% of cases occur below he age of 1 year). Complications as empyema and pyopneumothorax are so common that they are considered as a part of the clinical picture.

c) Streptococcal pneumonia: It mainly occurs between 3-5 years. It is midway in severity between pneumococcal pneumonia and staphylococcal pneumonia. Laboratory confirmation is by the elevated ASO titer.

d) Hemophilus influenza pneumonia: It is characterized by an insidious onset and prolonged course. It is an important cause of lobar pneumonia in children below the age of 2 - 3 years. Complications as pleural effusion are common.

Differentiating features between bacterial and viral pneumonias

	Bacterial pneumonia	Viral pneumonia
Pathological type	Lobar or bronchopneumonia	Bronchopneumonia or interstitial
Clinical data		
Temperature	High (above 39.5°C)	Mild or moderate (below 38.5°)
Toxicity	Marked	Minimal
Cough	Not severe	Severe and may be spasmodic
Complications	Common	Uncommon
Laboratory data		
Leukocytic count	Above 15.000 (granulocytes)	Below 15.000 (lymphocytes)
Bandemia	Common	Unusual
Toxic granulations	Common	Unusual
CRP	Elevated (above 20 mg/liter)	Normal
ESR	Elevated (above 30 mm/first hour)	Normal
Blood culture	May be positive	Negative
Chest x-ray	Lobar consolidation or Patchy infiltrate	Reticulonodular infiltrate or Parahilar peribronchial infiltrate

e. *Other agents:* Several other bacteria as klebsiella, pseudomonas, E. coli and enterobacter can be responsible especially in infants and in those with immunodeficiency. Pseudomonas pneumonia is particularly common nosocomial pneumonia in mechanically ventilated patients.

Accurate identification of the causative organism can be made by blood culture, culture of tracheal aspirate or culture of associated pleural effusion. Urgent therapy is indicated without waiting for the results.

2. Viral pneumonia: It is usually bronchopneumonia or interstitial pneumonia. The possibility should be considered when the fever is mild or moderate and the patient does not look sick. Simple investigations and chest x-ray are useful for differentiation from bacterial pneumonia (see above).

3. Mycoplasma pneumonia: It has a rather characteristic picture: (1) It is mainly seen in school-age children, (2) severe spasmodic cough is the main symptom and the patient has no respiratory distress, (3) Chest auscultation reveals a lobar pneumonia with bronchial breathing and fine crepitations over the involved lobe, (4) Chest x-ray reveals lobar consolidation or lobar reticulonodular infiltrate. Diagnosis can be confirmed by the presence of high titer of cold agglutinins.

Respiratory presentations of mycoplasma infection

Pertussis-like illness (see acute prolonged cough).
Bronchiolitis-like illness (see acute bronchiolitis).
Mycoplasma lobar pneumonia.

4. Pneumocystis carinii pneumonia: It is a severe interstitial pneumonia caused by pneumocystis carinii and characterized by presence of plasma cells (interstitial plasma cell pneumonia). It mainly occurs in prematures, young infants, mechanically ventilated patients and immunocompromized patients. The condition should be suspected in every case of persistent pneumonia over weeks (slowly resolving pneumonia).

Causes of prolonged or persistent pneumonia (slowly resolving pneumonia)

Resistant severe bacterial pneumonia (staphylococcal, pseudomonas, others).
Viral interstitial pneumonia (especially with adenovirus infection).
Pneumocystis carinii (plasma cell) pneumonia.
Fungal pneumonia (especially with candida albicans).
Immunodeficiency.
Anatomical abnormalities.

3. What are the complications?

Several complications may occur especially in infants and young children. Complications are much commoner with bacterial pneumonias, and can be classified into 2 groups, pulmonary and extrapulmonary complications.

Complications of pneumonia

Pulmonary complications

- Pleural effusion, empyema or pyopneumothorax (see Basic Pediatric Radiology).
- Respiratory failure: Especially with severe bacterial bronchopneumonia in infants.
- Pulmonary edema: Especially with fulminant bacterial pneumonia.
- Lung abscess: Especially with klebsiella pneumonia or staphylococcal pneumonia.

Extrapulmonary complications

- Toxic myocarditis and acute congestive heart failure.
- Functional paralytic ileus (vomiting, abdominal distention).
- Septicemia and may be septic shock.
- Meningismus (neck rigidity) especially with upper lobe pneumonia.

6. Recurrent Chest Infection

Cardiac causes	Pulmonary causes	Immunodeficiency
Plethoric lung field	Recurrent aspiration	**Primary immunodeficiency**
Atrial septal defect	Foreign body inhalation	Lymphocyte deficiency
Ventricular septal defect	Chronic infections	Phagocyte deficiency
Patent ductus arteriosus	Chronic sinusitis	Complement deficiency
Endomyocardial disease	Tuberculosis	**Secondary immunodeficiency**
Endocardial fibroelastosis	Bronchiectasis	Infections
Congestive cardiomyopathy	Chronic genetic diseases	Malnutrition
Genetic cardiomyopathy	Immotile cilia syndrome	Other causes

The frequent complaint of parents that the child is having recurrent chest infection and poor resistance requires careful evaluation. In normal infants and children, 6 - 8 acute respiratory illnesses per year is not unusual where the recurrent infections are simply caused by ***repealed exposure to infectious agents.***

However, when the recurrent infections are unusually more frequent or unusually severe (as recurrent pneumonia), the following groups should be considered.

A) CARDIAC CAUSES

Cardiac causes should be routinely excluded in every case of unusually recurrent chest infection.

1. Plethoric lung fields: Congenital noncyanotic heart diseases with left-to-right shunt and plethoric lung fields are commonly associated with unusually recurrent chest infection. ASD, VSD and PDA are clinically evident by their characteristic murmurs. Diagnosis is confirmed by chest x-ray and echocardiography.

2. Endomyocardial diseases: When recurrent chest infection is accompanied with cardiomegaly and congestive heart failure, endomyocardial diseases as endocardial fibroelastosis and congestive cardiomyopathy should be considered (see congenital heart diseases).

B) PULMONARY CAUSES

Many of the causes of chronic cough can present clinically with recurrent chest infection. The most important of these causes are:

1. Recurrent aspiration: Recurrent aspiration during feeding is an important cause in infancy. Gastroesophageal reflux is the most common but other causes, as tracheoesophageal fistula and cricopharyngeal incoordination should be also considered. Barium swallow under screen can differentiate between these conditions.

2. Foreign body inhalation: The possibility of foreign body inhalation should be considered especially in young children. The suspicion is considerable if the onset of the first episode was associated with spasmodic cough and choking and chest examination reveals an asymmetric air entry. Chest x-ray may reveal obstructive emphysema or collapse. Diagnosis is made by bronchoscopy.

3. Chronic infections: ***Chronic sinusitis*** is an important cause of recurrent chest infection that should be routinely excluded. ***Pulmonary tuberculosis*** is also an important cause especially in low socioeconomic classes and in unvaccinated children. The condition should be strongly suspected when the illness is associated with prolonged fever, weight loss or lymphadenopathy. Chest x-ray can reveal dense hilar shallow, lobar consolidation or pulmonary infiltrate. Strongly positive tuberculin test and high ESR are important suggestive findings. The demonstration of acid-fast bacilli in stained smears (gastric lavage or bronchial secretions) is diagnostic. Rapid diagnosis can be made by polymerase chain reaction (PCR). ***Bronchiectasis*** is a chronic suppurative lung disease characterized by a permanent dilatation and destruction of the bronchial and peribronchial tissues with subsequent development of lung fibrosis. It can be congenital or acquired and localized or generalized. *Congenital bronchiectasis* is rare and it occurs due to an arrest in bronchial development leading to formation of multiple cysts. *Acquired bronchiectasis* accounts for the majority of cases and it occurs secondary to chronic sinusitis, tuberculosis, cystic fibrosis, immotile cilia syndrome, bronchial asthma, foreign body inhalation or immunodeficiency. As bronchiectasis is characteristically a disease of remissions and exacerbations, recurrent chest infection is the main presentation. During acute episodes, cough and expectoration of copius mucopurulent sputum are the main symptoms. Chest examination usually reveals fine or moist crepitations and sometimes wheezing. Clubbing of fingers may appear in longstanding cases (more than 1 year) in addition to growth retardation and persistent dyspnea. Chest x-ray may reveal a reticular, reticulonodular or parahilar-peribronchial infiltrate (not pathognomonic). Diagnosis was traditionally made by bronchoscopy and bronchography. Recently, thin-section high-resolution CT scan of the chest has replaced bronchography because it is more sensitive and less invasive. It can clearly demonstrate the cylindrical and cystic changes.

4. Chronic genetic diseases: Cystic fibrosis, alpha one antitrypsin deficiency and immotile cilia syndrome are rare causes. The possibility should be considered when the family history is positive and the illness is presenting in infancy.

C) IMMUNODEFICIENCY

Immunodeficiency is clinically suspected in case of unusually recurrent or unusually severe infections. In this condition, recurrent infections are not limited to the chest but usually involving the gastrointestinal tract, urinary tract and skin. It is important to emphasize that the diagnosis of immunodeficiency should never be made without laboratory confirmation of immunodeficiency.

Disorders causing immunodeficiency are either primary (inherited) or secondary (acquired) and can affect one or more of the 3 major components of the immune system the lymphocytes, the phagocytes and the complement system.

(a) Primary (inherited) immunodeficiency

These disorders can involve the lymphocytes, phagocytes or the complement system. Lymphocyte immunodeficiency is the most common and it can affect B-cells, T-cells or both. The type of infection can suggest the underlying immunodeficiency.

Primary immunodeficiency

Immunodeficiency	Relative distribution	Type of infections
B-cell immunodeficiency	50%	Bacterial and giardia infections
T-cell immunodeficiency	30%	Viral and fungal infections
Complement immunodeficiency	18%	Bacterial infections
Phagocyte immunodeficiency	2%	Bacterial skin infections

1. Lymphocyte immunodeficiency: It accounts for 80% of cases of primary immunodeficiency (50% B-cells and 30% T-cells and both cells).

a) B-cell immunodeficiency: It is also called humoral or antibody deficiency.

- The main causes are x-linked agammaglobulinemia (Bruton disease), autosomal recessive agammaglobulinemia, common variable immunodeficiency (AR, AD) and selective deficiencies of immunoglobulins (selective IgA deficiency, selective IgM deficiency and selective IgG subclass deficiency). It is important to mention that selective deficiencies are about 100 times more common than total deficiencies.
- The main clinical presentation is *recurrent bacterial and giardia lamblia infections.*
- Laboratory diagnosis can be made by both screening and diagnostic tests. *Screening test* is made by quantitative measurement of serum immunoglobulins (see below). *Diagnostic tests* are indicated when screening test is inconclusive or equivocal. Quantitative enumeration of B-cells in peripheral blood can be made depending on the presence of surface receptors for immunoglobulins or complement (B-cells are absent in Bruton disease and present in common variable immunodeficiency). Measurement of T_4 (T-helper) and T_8 (T-suppressor) activity is also important. Deficient T_4 and excess T_8 are responsible for the increased susceptibility to infections. Specific antibody response can be tested by measuring the antibody response to a specific antigen (as antigens of immunization procedures).

Serum immunoglobulins

Immunoglobulins	Normal range	Diagnostic level of deficiency
Total Immunoglobulins	750-1800 mg/dl	Below 250 mg/dl
IgG	700- 1400 mg/dl	Below 200 mg/dl
IgM	30- 200 mg/dl	Below 10 mg/dl
IgA	30 - 200 mg/dl	Below 5 mg/dl

b) T-cell and combined T and B immunodeficiency: T-cell deficiency is also called cell-mediated or cellular immunodeficiency. Since T-cells have an important role on B-cell differentiation and function, T-cell deficiency results in deficiency of both T-cell and B-cell functions.

• The disorders causing T-cell deficiency include severe combined immunodeficiency (SCID), combined immunodeficiency (CID) and immunodeficiency with other major defects (Wiskott Aldrich syndrome, Di George syndrome, letterer Siwe syndrome and ataxia telangiectasia). SCID can be sporadic, x-linked or autosomal recessive and is characterized by absent T-cell function. CID is a milder form characterized by low but not absent T-cell function.

• The main clinical presentation of T-cell deficiency is *severe recurrent viral and fungal infections*. Systemic illness following BCG or measles vaccination is another clinical presentation.

• Laboratory diagnosis can be made by both screening and diagnostic tests. *Screening tests* include total lymphocyte count (count below 1200/cmm is suggestive), delayed hypersensitivity skin test as tuberculin test (induration less than 5 mm is suggestive) and lateral chest x-ray to demonstrate thymus (absent thymic shadow in neonates is suggestive). *Diagnostic tests* are indicated when screening tests are suggestive. Quantitative enumeration of T-cells in peripheral blood is the main test. Mature T-cells have the property of binding in vitro to sheep erythrocytes to form rosettes (erythrocyte rosette formation). Normally, the percentage of rosette forming cells is 80%. Counts below 20% indicate a primary T-cell immunodeficiency, while counts between 20 - 45% occur with viral infections, autoimmune diseases and malignancy. Enumeration of subpopulation of T-cells (T_4, T_8) can be made by monoclonal antibodies. Specific T-cell functions can be also assessed by different assays. T-cytotoxic activity is assessed by a test called "cell mediated lympholysis". T-helper, T-suppressor, T-lymphokine producing and T-memory functions can be also assessed by specific tests.

Laboratory evaluation of B-cell and T-cell function

Test	B-cell function	T-cell function
Screening tests	Serum immunoglobulins (Total and selective)	Total lymphocyte count Tuberculin test Lateral chest x-ray on thymus
Diagnostic tests	Enumeration of B-cells Enumeration of T_4 and T_8 Specific antibody response	Enumeration of T-cells Enumeration of T_4 and T_8 Specific T cell functions

2. Complement immunodeficiency: It forms 18% of primary immunodeficiency.

• Deficiency of C3 and C5 result in *severe recurrent bacterial infections* while deficiency of late components (C6, C7, C8) result in recurrent gonococcal and meningococcal infections. Deficiency of early components (Cl, C4, C2) results in a symptom complex resembling systemic lupus erythematosus (SLE).

- Laboratory diagnosis can be made by both screening and diagnostic tests. *Hemolytic complement assay (HC50)* is the mainly used screening test and it depends on the ability of the 9 components to interact and lyse the antibody-coated erythrocytes. The dilution of the serum, which lyses 50% of cells, determines the end point. In congenital complement deficiencies the values are almost zero, while in acquired deficiencies, values vary according to the severity of the underlying disease. *Determination of serum level of all complement components* (especially C3) is also available and can diagnose selective deficiency of any component.

3. Phagocyte immunodeficiency: It accounts for only 2% of cases of primary immunodeficiency.

- Disorders of phagocytes are either neutropenia or leukocyte dysfunction. ***Inherited neutropenias*** include infantile lethal agranulocytosis (AR) and cyclic neutropenia (AD). ***Leukocyte dysfunctions*** include disorders of chemotaxis (migration of leukocytes into the inflamed area) and disorders of intracellular killing of bacteria.
- The main clinical presentation of phagocyte immunodeficiency is *recurrent pyogenic skin infections.*
- Laboratory diagnosis of phagocyte deficiency is made through evaluation of leukocyte number and function. *Severe neutropenia* (count below 2000/cmm) is the basic defect in infantile lethal agranulocytosis (familial neutropenia) and cyclic neutropenia. A compensatory monocytosis and eosinophilia is usually present. *Leukocyte function* can be assessed by tests of chemotaxis and cytochemical tests. Chronic granulomatous disease (X-linked) is diagnosed by Nitroblue tetrazolium test (NBT test). Failure to reduce the dye is detected in all cases and in asymptomatic mothers. Chediak-Higashi syndrome is characterized by the presence of abnormal leukocyte giant granules. Myeloperoxidase test and leukocyte alkaline phosphatase test are also simple and useful tests.

Leukocyte dysfunction

Disorders of chemotaxis	Disorders of intracellular killing
Leukocyte adhesion deficiency	Chronic granulomatous disease
Specific granule deficiency	Chediak-Higashi syndrome
Hyperimmunoglobulin E syndrome or (JOB syndrome)	Myeloperoxidase deficiency
Kartagener syndrome	Leukocyte alkaline phosphatase deficiency
Shwachman syndrome	Leukocyte G6PD deficiency
	Bilobed nucleus and absent granules

(b) Secondary (acquired) immunodeficiency

Acquired disorders are much commoner than inherited disorders. The type and degree of immunodeficiency as well as the outcome depend on the causative disease.

1. Infections: Severe bacterial or viral infections are a common cause of transient complement and phagocyte deficiencies (both chemotaxis and intracellular killing of organisms are impaired).

• ***Human immunodeficiency virus (HIV) infection*** *(AIDS or acquired immunodeficiency syndrome)* is a serious potentially fatal infection characterized by profound immunodeficiency especially of the T-cell function (the virus primarily causes destruction of T_4 cells). Although the disease is only discovered in 1981, the incidence is rapidly rising allover the world. In pediatric age group, the disease is mainly acquired through perinatal transmission from an infected mother. Postnatal infection may also occur through blood transfusion. Clinical manifestations in childhood include: (1) *Nonspecific manifestations* as lymphadenopathy (90%), hepatosplenomegaly (85%), and failure to thrive (62%), (2) *Progressive neurological disease* as diffuse encephalopathy, microcephaly and cerebral atrophy, (3) *Lymphoid interstitial pneumonitis* with its typical pulmonary infiltrate (parahilar peribronchial), (4) *Recurrent secondary infections* (bacterial, viral, fungal, mycoplasma and opportunistic), (5) *Secondary cancer* including lymphoma and Kaposi sarcoma and (6) *Other conditions* as cardiomyopathy, nephropathy and hepatitis. Laboratory diagnosis depends on the serological detection of antibodies to HIV. Abnormalities in immune function include decreased T_4/T_8 ratio and increased immunoglobulins (above 1800 mg/dl).

Pediatric HIV classification

	Clinical Categories			
Immune Categories	**N** (No disease)	**A** (Mild disease)	**B** (Moderate disease)	**C** (Severe disease)
1. No evidence of suppression	N1	A1	B1	C1
2. Moderate suppression	N2	A2	B2	C2
3. Severe suppression	N3	A3	B3	C3

No disease means no symptoms or signs of illness.

2. Protein-calorie malnutrition: Severe protein-calorie malnutrition is the most common cause of severe immunodeficiency in underdeveloped countries. The immunodeficiency is involving the 3 major components (lymphocyte, phagocyte and complement deficiencies).

3. Other causes: The main other causes are:

a) Malignancies especially those with bone marrow infiltration as leukemia, lymphoma and neuroblastoma.

b) Hematological diseases especially aplastic pancytopenia. Functional hyposplenism may occur in sickle cell anemia.

c) Hypoproteinemia especially with nephrotic syndrome, chronic diarrhea and protein losing enteropathy.

d) Iatrogenic causes: Prolonged corticosteroid therapy and antineoplastic drugs result in impairment of immune function. Splenectomy is also followed by severe infections due to loss of fixed phagocytes (macrophages) of the spleen.

8

Digestive System

- **Abdominal Examination.**
1. **Refusal of Feeding.**
2. **Vomiting.**
3. **Abdominal Pain.**
4. **Diarrhea.**
5. **Constipation.**
6. **Gastrointestinal Bleeding.**
7. **Abdominal Enlargement.**
8. **Hepatic and Splenic Enlargement.**
9. **Jaundice.**

Abdominal Examination

Inspection: Abdominal enlargement, abdominal movements, other findings
Palpation: Tenderness or rigidity, enlarged organs or abdominal masses
Percussion: Differentiation between abdominal distension and ascites
Auscultation: Lost intestinal sounds in paralytic ileus

Clinical assessment of the digestive system should include ***symptoms of dysfunction*** (anorexia, vomiting, diarrhea, constipation, abdominal pain, gastrointestinal bleeding and jaundice), ***extraabdominal examination*** (jaundice, wasting, edema, bleeding and examination of oral cavity) and ***abdominal examination,*** which is made in 4 steps:

1. Inspection

It is important for detection of:

1. Abdominal enlargement: Large abdomen may be due to:

a) Abdominal distension where the enlargement is due to distension of intestinal loops or colon by gases. Intestinal obstruction and malabsorption are the main causes.

b) Abdominal masses where the enlargement is due to enlarged organs or other abdominal masses. Hepatosplenomegaly, renal and suprarenal masses are the most common.

c) Ascites where the enlargement is due to presence of free fluid in the peritoneal space. Hypoproteinemia, portal hypertension and local peritoneal causes are the most common.

Differentiation between these entities is made by palpation and percussion.

2. Abdominal movements with respiration: Normally the abdomen distends during inspiration and collapses during expiration. With diaphragmatic paralysis, the reverse occurs leading to paradoxical breathing or seesaw movements (see acute paralysis).

3. Other findings: Dilated abdominal wall veins is a sign of collateral circulation and it indicates the presence of portal hypertension. Other important findings include umbilical or inguinal hernia, divarication of recti and skin lesions as purpuric eruption, pigmentation or scar of previous operation.

2. Palpation

Palpation should be made while the abdomen is relaxed. Slight flexion of the hips and distraction of the child's attention by talking or conversation are helpful. In crying infants, palpation can be made immediately after crying while the infant is taking a deep inspiration. When history of abdominal pain is present the painful area should be palpated last. Palpation is useful for detection of:

1. Tenderness or rigidity: Location of the area of maximal tenderness is diagnostically important. Tenderness can be elicited in the right hypochondrium (hepatitis or congested hepatomegaly of congestive heart failure), right iliac fossa (appendicitis), epigastric area (gastritis), left hypochondrium (splenic congestion), left lumbar and left iliac fossa (colitis) or loin (perinephric abscess). Diffuse or generalized tenderness occurs with peritonitis.

2. Enlarged organs or abdominal masses: Hepatic and/or splenic enlargement is common. Comment should include the *size* (in centimeters below the costal margin in midclavicular line), *consistency* (soft, firm or hard), *surface* (smooth or irregular) and *lower border* (sharp or rounded). Palpation of the spleen should include the splenic notch. The degree of enlargement can be classified as mild (confined to hypochondrial area), moderate (reaching lumbar area) or massive (reaching iliac fossa). Palpation of the kidney by both hands is also important. Other abdominal masses may be accidentally discovered. The comment on any mass should include its location, size, consistency, surface and movement (see abdominal masses).

3. Percussion

Normally, a tympanic resonance is heard on abdominal percussion. Percussion is mainly useful for:

1. Differentiation between abdominal distention and ascites: With abdominal distension, there is hyperresonance on percussion. With ascites, *shifting dullness* can be elicited (dullness in the flank while the patient in supine position and resonance in the same area when the patient lies on his side). With a minimal ascites, shifting dullness can be elicited in knee chest position. With massive ascites, *transmitted fluid wave* can be palpated with one hand placed on one side while the other is tapping on the opposite flank.

2. Confirmation of enlarged organs: This is particularly important when the abdomen is tense or rigid and palpation is difficult. In this case, dullness can be elicited over the enlarged organ.

4. Auscultation

It is only useful in paralytic ileus where the normally heard intestinal sounds are lost. This is an important differentiating point between mechanical and functional intestinal obstruction.

1. Refusal of Feeding

Painful oral lesions	Anorexia
Monilial stomatitis	Acute transient anorexia
Herpetic stomatitis	Chronic physiological anorexia
Herpangina	Chronic organic anorexia
Hand, foot and mouth disease	Chronic infections
Aphthous ulcers	Chronic inflammation
Eruption gingivitis	Chronic systemic diseases
Acute necrotizing ulcerative gingivitis	Malignancy

Trismus (lock jaw) is a rare cause, but an important sign of tetanus

The frequent complaint of parents that the infant or the child is refusing to eat is mainly caused by 2 conditions; painful oral lesions and poor appetite or anorexia.

A) PAINFUL ORAL LESIONS

Inflammation of oral mucosa (stomatitis) is a common clinical problem especially in infants and young children. When inflammation is also involving the gums, the term gingivostomatitis can be used. Gingivitis means inflammation of gums with no or minimal affection of the oral mucosa.

1. Monilial stomatitis (Thrush or oral candidiasis): It is an acute infection of oral cavity caused by candida albicans. It is characterized by:

- It is most common in neonatal period and early infancy where the infection can be acquired at birth or from infected nipple in breast fed infants. The condition is also common with prolonged antibiotic therapy, malnutrition and T-cell immunodeficiency.
- Clinically, there is a white flaky plaques covering all or part of the *tongue, gingiva and oral mucosa.* These plaques when removed leave a bright inflamed base. The condition is mildly painful and may cause feeding difficulty.
- The condition usually subsides within one week of effective therapy with oral nystatin or miconazole. Persistent oral moniliasis for more than 10 days in spite of the effective therapy or frequently recurrent lesions should raise the possibility of immunodeficiency and T-cell function should be evaluated (see recurrent chest infection).

2. Herpetic gingivostomatitis (ulcerative stomatitis): It is an acute infection of the oral cavity caused by herpes simplex virus. It is characterized by:

- It is most common in children between the ages of 1 - 3 years.
- Clinically, the condition starts with high fever, severe mouth pain, salivation and refusal of feeding. Examination of oral cavity reveals small ulcers (2-10 mm in diameter) over the *tongue, gingiva and oral mucosa.* In severe cases, ulcers may involve all oral mucosa.

- The condition usually lasts for 4-8 days. Pain usually disappears few days before complete healing of ulcers.
- It is the most common cause of gingivitis and mouth ulceration. Other causes of ulceration especially herpangina should be considered.

3. Herpangina: It is an acute infection of the oral cavity caused by coxsackie-virus. It is characterized by:

- It is mostly seen in children below the age of 5 years.
- Clinically, the illness starts with fever, sore throat and refusal of feeding. Examination of oral cavity reveals discrete vesicles and ulcers mainly located on the *anterior tonsillar pillars*. The ulcers are characteristically small in size (1-5 mm in diameter) and few in number (usually 1 -5), and each one is surrounded by an erythematous ring. In severe cases, fever is high and the ulcers may involve the soft palate, uvula, tonsils and posterior pharyngeal wall and their number may reach up to 15.
- The condition usually subsides spontaneously over 3 - 6 days.

4. Hand, foot and mouth disease: It is another acute disease caused by coxsackievirus. It is characterized by:

- Vesicles and ulceration in the mouth mainly on the tongue and oral mucosa.
- Vesicles on the hands and feet mainly on the dorsal surface.
- Transient erythematous rash on the buttocks is also common.

5. Aphthous ulcers (canker sores): It is a condition of unknown etiology, probably an autoimmune disease, with a tendency to recurrence. It is characterized by a solitary or few ulcers mainly located in the floor of the mouth, ventral surface of the tongue and the mucobuccal fold. The ulcer is usually small (less than 5 mm) with a depressed center and erythematous periphery. The ulcers are painful and may interfere with feeding. Healing usually occurs in less than a week.

6. Eruption gingivitis: Difficult teething in dentulous infants may lead to gingival inflammation around the erupted tooth or teeth. Bacterial invasion may be responsible for the commonly associated fever, irritability and loose bowel movements.

7. Acute necrotizing ulcerative gingivitis (ANUG): It is an acute serious infection of gingiva mostly caused by a mixture of organisms (spirochetes and fusobacteria). It is characterized by:

- It mainly occurs in malnourished children, and it is rare in healthy individuals.
- Clinically, it is characterized by fever, necrosis and ulceration of gingiva with adherent grayish pseudomembrane over the affected gingiva. Fetor oris and cervical lymphadenopathy are common. The lesions may extend to adjacent tissues causing necrosis of facial structures (cancrum oris or noma).
- The condition responds dramatically to antibiotic therapy (penicillin or erythromycin), local antiseptic measures and analgesics.

Geographic tongue is a common benign condition, which is commonly misdiagnosed as oral moniliasis or herpetic gingivostomatitis. It is characterized by the presence of one or more bright red patches with whitish or grayish margin upon the dorsum of an otherwise normally roughened tongue. The patches look like a map (geographic tongue). The condition is asymptomatic and may persist for several weeks or months. Recurrences are common and treatment is not required.

B) ANOREXIA

Loss of appetite (anorexia) is a common problem in pediatric practice, which can be acute or chronic.

1. Acute transient anorexia: Transient loss of appetite is a very common associated finding in acute bacterial or viral infection. The anorexia usually accompanies the illness and the appetite returns to normal with the control of infection.

2. Chronic physiological (false) anorexia: Most children between 1-6 years do not eat amounts that satisfy their parents. This is because of the normal decrease in caloric requirements and growth during this period. Parents usually compare between the infant's appetite during the first year and his appetite thereafter and wrongly misinterpret it as anorexia. Parental pressure for eating usually complicates matters as some children may respond by more refusals. These children are usually normal, active and with average weight for age and sex. As anorexia is the only complaint, examination reveals no abnormality. Reassurance and refusal of prescribing any medication are important.

3. Chronic organic (true) anorexia: Anorexia may accompany a long list of chronic diseases as chronic infections, rheumatic diseases, chronic renal or hepatic failure and malignancy. In these conditions, anorexia is not the only complaint and other symptoms as prolonged fever, weight loss or poor activity are usually present. Examination commonly reveals abnormal findings as underweight, anemia, fever, lymphadenopathy or organomegaly. Treatment is the treatment of the causative disease.

2. Vomiting

Acute Vomiting	Chronic vomiting
Acute infections	**Causes in infancy**
Focal infections	Dietetic causes
Septicemia	Gastrointestinal dysfunction
Acute metabolic conditions	Chronic metabolic conditions
Reye syndrome	**Causes in childhood**
Diabetic ketoacidosis	Increased intracranial pressure
Acute intestinal obstruction	Peptic ulcer
Mechanical obstruction	Chronic renal failure
Functional obstruction (ileus)	

Vomiting is a very common complaint especially in infants and young children. According to severity and duration, vomiting can be classified into acute (lasts for few days) and chronic (remains for weeks or months). It is important to remember that vomiting is a non-localizing symptom and other clinical manifestations are needed to identify the cause.

A) ACUTE VOMITING

Most cases of acute vomiting in infants and children are caused by acute infections. However, other causes especially acute metabolic conditions and acute intestinal obstruction should be always in mind.

1. Acute infections: Presence of fever is an important clue for infection. According to presence or absence of other localizing signs, infections can be classified as focal infections or septicemia.

a) Focal infections: *Acute CNS infections* with increased intracranial pressure, as meningitis and encephalitis should be always considered. *Respiratory infections* as bronchitis or pneumonia are commonly associated with post-tussive vomiting. With *abdominal infections*, abdominal pain is an important concomitant complaint. The clinical triad of fever, vomiting and abdominal pain should suggest early gastroenteritis as a first possibility. Other possibilities include streptococcal pharyngitis, appendicitis, pyelonephritis, early hepatitis and pancreatitis (see also acute abdominal pain).

b) Septicemia: In absence of any localizing signs, severe persistent vomiting and high fever should suggest the diagnosis of septicemia. The patient looks critically sick with toxic look, cold extremities (shock) and may be disturbed consciousness. Immediate hospitalization, investigations and parenteral antibiotic therapy are indicated.

2. Acute metabolic conditions: With ***Reye syndrome*** (acute encephalopathy with fatty infiltration of the liver), the acute vomiting is rapidly followed by altered consciousness. Hepatomegaly is clinically evident. With ***diabetic ketoacidosis,*** polyuria, vomiting, dehydration, acidosis and altered consciousness are the main presenting features. ***Acute drug intoxication*** should be also considered. Digitalis toxicity should be considered in patients receiving digoxin.

3. Acute intestinal obstruction: Persistent vomiting with constipation or abdominal distention should suggest the possibility of intestinal obstruction. Greenish bile-stained vomitus is a definite sign of obstruction. Plain x-ray of the abdomen (erect position) can demonstrate the multiple air-fluid levels. Intestinal obstruction can be mechanical or functional (see acute abdominal pain and abdominal distension).

B) CHRONIC VOMITING

(a) Causes in infancy

1. Dietetic causes: ***Overfeeding*** is an important cause that should be always considered. The infant is usually overweight for his age and associated findings as abdominal colic or loose bowel movements are common. ***Cow's milk allergy*** should be also considered in formula-fed infants.

2. Upper gastrointestinal dysfunction as gastroesophageal reflux, hiatus hernia, achalasia or incomplete obstruction (pyloric stenosis and duodenal stenosis) should be considered. Barium swallow and barium meal are essential for diagnosis.

3. Chronic metabolic conditions as hypercalcemia (vitamin D intoxication), renal tubular acidosis, aminoacidopathies, organic acidemias and hyperammonemia should be considered. Failure to thrive is an important clue for suspicion. Metabolic screening should include serum calcium, acid-base balance, ammonia level and urinary screening for aminoacidopathies.

(b) Causes in childhood

1. Increased intracranial pressure: Persistent morning vomiting, morning headache and blurring of vision should suggest increased intracranial pressure and CT scan of the head is important to exclude brain tumours or other space-occupying lesions (see common malignancies).

2. Peptic ulcer: Chronic vomiting following feeding and associated with epigastric pain should suggest the possibility. Endoscopy is essential for diagnosis.

3. Chronic renal failure: Chronic vomiting, anemia and growth failure may be the initial presentations. Evaluation of renal function (blood urea and creatinine) is an important step in every case of chronic vomiting.

3. Abdominal Pain

Acute abdominal pain	Recurrent abdominal pain
Acute abdominal infections	Dysfunctional recurrent abdominal pain
Acute medical conditions	Organic recurrent abdominal pain
Acute intestinal obstruction	

Abdominal pain is one of the most common complaints in pediatric practice. Clinically, it can be classified into acute and recurrent.

A) ACUTE ABDOMINAL PAIN

Causes of acute abdominal pain are nearly the same causes of acute vomiting. Acute abdominal infections are by far the most common causes.

Causes of acute abdominal pain

Acute abdominal infections	Acute medical conditions	Acute Intestinal obstruction
Streptococcal pharyngitis	Henoch-Schonlein vasculitis	Incarcerated inguinal hernia
Early gastroenteritis	Right lower lobe pneumonia	Intussusception
Early hepatitis	Acute rheumatic fever	Volvulus
Acute appendicitis	Diabetic ketoacidosis	Postoperative adhesions
Acute pyelonephritis	Splenic infarction	Impacted fecal masses
Acute pancreatitis	Drug intoxication	Round worm masses
Acute peritonitis	Acute hepatic porphyria	Acute peritonitis

1. Acute abdominal infections: As mentioned with acute vomiting, the clinical triad of fever, vomiting and abdominal pain should suggest the following possibilities:

a) Streptococcal pharyngitis: It commonly presents with fever, sore throat and abdominal pain. The abdominal pain is caused by the commonly associated mesenteric adenitis.

b) Early gastroenteritis: Fever, vomiting and abdominal pain are usually the initial manifestations of gastroenteritis Diarrhea usually appears within 24 hours.

c) Early hepatitis: Anorexia, mild fever, vomiting and abdominal pain should suggest early or preicteric hepatitis. Inspection of the urine for dark coloration (bilirubinuria) is an important simple test. Jaundice usually appears after 4 - 6 days and liver becomes enlarged and tender.

d) Acute appendicitis: It should be considered in every case of acute abdominal pain in children. The pain is usually not severe and abdominal examination reveals a tender

right iliac fossa. When the abdominal pain is severe, the patient is probably not having acute appendicitis. Leukocytosis is an important confirmatory finding. In equivocal cases, re-evaluation after 6 hours is helpful. In true appendicitis, these 6 hours are sufficient to clarify the picture and diagnostic signs become well evident. When the diagnosis is delayed for more than 36 hours, the risk of perforation and peritonitis is great.

e) Acute pyelonephritis: High fever with rigors and abdominal pain should suggest the diagnosis. Tenderness over the loin may be elicited.

f) Acute pancreatitis: Fever, persistent vomiting and epigastric pain should suggest the diagnosis. The pain and vomiting usually increase during the first 2 days and the patient may need hospitalization. Diagnosis is confirmed by the elevated serum amylase level. Abdominal ultrasound is also very useful in demonstrating pancreatic enlargement, edema or abscesses. Viral infections especially mumps are the most common causes. Drugs (as diuretics, corticosteroids, paracetamol, sulfonamides and valproic acid) and blunt abdominal trauma are also common causes.

g) Acute peritonitis: Acute bacterial infection of the peritoneum can be primary or secondary. *Acute primary peritonitis* occurs in children with ascites due to nephrosis or cirrhosis and the infection is acquired through bacteremia or septicemia. The main invading organisms are pneumococci, streptococci and E. coli. *Acute secondary peritonitis* occurs through rupture of an intraabdominal viscus as with neglected appendicitis, incarcerated hernia, intussusception or volvulus. The invading organisms are the normal aerobic and anaerobic flora of the gastrointestinal tract. Clinically, fever, vomiting and diffuse abdominal pain are the initial presentations. Abdominal examination reveals a diffuse generalized tenderness with abdominal wall rigidity. With a perforated viscus, the patient looks seriously sick with toxic look, high fever and shock-like state. Polymorphonuclear leukocytosis is usually present and abdominal x-ray reveals functional (ileus) or mechanical intestinal obstruction. With a perforated viscus, pneumoperitoneum can be also demonstrated (see Basic Pediatric Radiology).

2. Acute medical conditions: Abdominal pain may accompany several other medical conditions. With *Henoch-Schonlein vasculitis*, abdominal pain and bleeding per rectum may occur but diagnosis is mainly based on the characteristic purpuric eruption. *Right lower lobe pneumonia* may be accompanied with referred abdominal pain. With *diabetic ketoacidosis*, abdominal pain and vomiting are common but polyuria, dehydration, acidosis and altered consciousness are the main presenting features. *Acute rheumatic fever* may be accompanied with acute abdominal pain. *Splenic infarction* is rare but should be considered when abdominal pain is associated with left hypochondrial tenderness. *Acute drug intoxication* should be also considered *Acute hepatic porphyria* is very rare below the age of 10 years.

3. Acute intestinal obstruction: Persistent vomiting with constipation or abdominal distension should raise the possibility. Greenish bile-stained vomitus is a definite sign of obstruction. In mechanical intestinal obstruction, colicky periumbilical

pain is usually present and bowel sounds are also present (with functional obstruction both abdominal pain and bowel sounds are absent). The most important causes of mechanical obstruction are:

a) Incarcerated inguinal hernia: Examination of hernial orifices and scrotum should be a routine step in every case of acute abdomen. Failure of reduction of an inguinal hernia is a surgical emergency.

b) Intussusception: It is the most common cause of intestinal obstruction between 3 months and 3 years with a peak incidence around the age of 6 months. The cause is unknown in most cases but occasionally it complicates gastroenteritis. The illness starts suddenly with *severe paroxysmal colicky abdominal pain* that recurs at frequent intervals and is accompanied with loud crying. Initially, the infant looks well and plays normally between the attacks. *Vomiting* occurs in most cases and is usually more frequent early. Within 12 - 24 hours of onset, most patients pass stool containing blood and mucus *(red currant jelly stool)*. At this point, the condition may be misdiagnosed as gastroenteritis with bloody diarrhea but absence of fever and the sudden onset of abdominal pain in an otherwise normal infant should suggest the diagnosis. Abdominal examination reveals a *sausage-shaped mass*, mostly in the right upper quadrant, in 70% of cases. The mass is better felt with bimanual abdominal and rectal examination. The presence of *bloody mucus on the finger* as it is withdrawn after rectal examination supports the diagnosis of intussusception. If the condition is not diagnosed early (during the first day or two), the infant will pass into a *shock-like state* with bile-stained vomiting, abdominal distension and high fever secondary td intestinal ischemia and gangrene. Plain x-ray of the abdomen may be useful and barium is occasionally needed (see Basic Pediatric Radiology). In early cases, simple reduction is the rule. In late cases, resection anastomosis is almost necessary.

c) Volvulus: The sudden appearance of vomiting, abdominal pain and abdominal distension should suggest the diagnosis. If the condition is not diagnosed early, bowel gangrene and bleeding per rectum occur. The illness is differentiated from intussusception by the early appearance of distension and the late appearance of bleeding. In intussusception, the reverse occurs (bleeding is early and distension is late).

d) Other causes: Acute intestinal obstruction may occur with several other conditions. Intestinal obstruction following abdominal surgery should suggest postoperative ileus, postoperative acute peritonitis or postoperative adhesions. Acute obstruction with a palpable abdominal mass may suggest an impacted fecal masses (sausage-shaped masses in the left lower quadrant), masses of round worms, tumor mass or mesenteric cyst. Acute peritonitis can lead to functional or mechanical obstruction (see above).

B) RECURRENT ABDOMINAL PAIN

Recurrent abdominal pain is a very common problem in pediatric practice that occurs in up to 10 -15% of children. In more than 90% of these children, no organic cause can be detected and the term dysfunctional or chronic nonspecific abdominal pain can be used. Clinical evaluation and differentiation between dysfunctional and organic recurrent abdominal pain require a careful history, thorough examination and some investigations.

Initial evaluation of children with recurrent abdominal pain

History

Abdominal pain: Site, severity, duration and frequency of the attacks.
Other complaints: Fever, vomiting, diarrhea, constipation, bleeding per rectum, weight loss or progression of symptoms.
Dietetic history: Types and amount of given foods.
History of drug intake: Especially salicylates and theophylline.
Family history: Stressful events as family problems, loss of one parent, delivery of new sibling or school phobias.

Examination

General examination: Appearance, temperature, body weight for age.
Abdominal examination: Tenderness, rigidity or palpable masses.

Simple investigations

Urine analysis: May reveal hematuria, crystalluria or infection.
Stool analysis: May reveal parasitic infestation or bleeding per rectum.
Complete blood count: May reveal anemia or leukocytosis.
Abdominal x-ray: May reveal urinary calculi or fecal impaction.

1. Dysfunctional recurrent abdominal pain: Fortunately, more than 90% of children with recurrent abdominal pain belong to this group. Other terms as ***"nonspecific"*** or ***"psychogenic"*** recurrent abdominal pain can be used. The term "irritable bowel syndrome" may be also applied. The true mechanism of pain is unknown but several factors may be responsible. Stressful events as family problems, loss of one parent, delivery of new sibling and school phobias are all important factors. Some children complain to gain more love and sympathy and others may imitate an adult with recurrent abdominal pain.

• The pain is usually *periumbilical* and the child can often locate the site even with one finger. It is usually vague, not severe (not interfering with activity) and subsides spontaneously in less than 20 minutes. As the pain is not severe, parents usually come to complain after several weeks of onset.

• There are no other associated complaints and the child appears normal and healthy. Abdominal examination is generally negative.

• Simple investigations as urine, stool, complete blood count and abdominal x-ray are all normal. Reassurance is important.

2. Organic recurrent abdominal pain: Fortunately, it accounts for only less than 10% of cases. Causes are diverse and related to different systems (see below). It is important to emphasize that serious malignancies do not present with recurrent abdominal pain.

• The pain is usually *away from the umbilicus*. The likehood of the pain to be organic is directly related to its distance from the umbilicus. The site of the pain may give a diagnostic clue as with chronic hepatitis (right hypochondrium), peptic ulcer (epigastric), chronic constipation (left lower quadrant) and renal calculi (loin pain).

• Other associated complaints are common and can guide the diagnosis. Diarrhea, constipation, bleeding per rectum, hematuria or dysuria and weight loss are the most relevant. Recurrent episodes of abdominal pain and fever should suggest familial Mediterranean fever (periodic peritonitis). With examination the child may appear anemic or wasted. Abdominal examination may reveal focal tenderness or enlarged organs.

• Simple investigations are commonly abnormal. Further investigations depend on the clinical suspicion and may include abdominal ultrasonography, gastrointestinal barium studies, endoscopy and intravenous pyelography.

Causes of organic recurrent abdominal pain

Common causes	Uncommon causes	Rare causes
Parasitic infestations	Peptic ulcer	Inflammatory bowel diseases
Chronic constipation	Chronic hepatitis	Familial Mediterranean fever
Overeating, bad selection of food	Meckel's diverticulum	Hepatic porphyria
Lactose intolerance	Renal calculi	Abdominal epilepsy
Chronic use of drugs	Sickle cell anemia	Gynecological problems

• Parasitic infestations include giardiasis, amaebiasis and ascariasis (but not oxyurius).

4. Diarrhea

Acute Diarrhea	Chronic diarrhea
Gastroenteritis	**Chronic infections**
Bacterial	Bacterial, parasitic, tuberculous.
Viral	**Postenteritis malabsorption**
Parasitic	Sugar intolerance, Milk allergy
Noninfectious diarrhea	**Chronic nonspecific diarrhea**
Dietetic diarrhea	**Other causes of malabsorption**
Drug induced diarrhea	Hepatic: Biliary atresia
Parenteral diarrhea	Pancreatic: Cystic fibrosis
	Intestinal: Several causes

Diarrhea is a very common problem especially in infants and young children. It is defined as a passage of loose bowel movements (LBM) due to increased water content of the stool. It is usually associated with increased number of bowel movements.

According to the duration, diarrhea is classified into acute (duration less than 2 weeks) and chronic (duration more than 2 - 3 weeks).

A) ACUTE DIARRHEA

Acute diarrhea accounts for more than 90% of cases of diarrhea. Gastroenteritis (cute infective enteritis) is by far the most common cause.

- How to diagnose gastroenteritis?
- What is the severity of diarrhea?
- What is the causative organism?
- What are the associated complications?

1. How to diagnose gastroenteritis?

Diagnosis of gastroenteritis is clinical and depends on the presence of acute diarrhea with or without fever and vomiting. However, diagnosis should be only made after clinical exclusion of other causes of acute diarrhea. Dietetic history, history of drug intake and symptoms of respiratory or urinary tract infection are important.

1. Dietetic diarrhea: It may follow recent change in the type of milk, concentrated formula or recent addition of new foods not suitable for the age of the infant. Detailed dietetic history is important. Food poisoning should be considered in older children with severe diarrhea. The possibility becomes greater when more than one member of the family are simultaneously affected.

2. Drug induced diarrhea: Most oral antibiotics especially ampicillin can cause acute diarrhea (antibiotic-associated diarrhea). Oral vitamins when given in big amount may also cause diarrhea.

3. Parenteral diarrhea: It is a diarrhea that occurs secondary to infections outside the gastrointestinal tract as respiratory and urinary tract infection. The cause of diarrhea is the increased intestinal movements (hypermotility) with the resultant decrease in transit time and water absorption. History is very important because some cases of bronchitis comes with the complaints of fever, vomiting (post-tussive) and diarrhea and are wrongly diagnosed as gastroenteritis.

It is important to emphasize that in all noninfectious diarrhea, the diarrhea is usually mild. Severe diarrhea is diagnostic of gastroenteritis.

2. What is the severity of diarrhea?

The ***number*** of bowel motions can be taken as a parameter for severity. Diarrhea can be mild (4-6 motions/day), moderate (6-10 motions/day) or severe (more than 10 motions/day). For proper assessment, the ***volume*** of motions and the ***characters*** of the stool should be also considered. Stool character can be described as formed, soft, loose, very loose, watery or bloody. Big volumes of watery diarrhea are serious and can easily lead to dehydration.

3. What is the causative organism?

Although accurate differentiation between bacterial, viral and parasitic gastroenteritis can not be made except by stool analysis and stool culture, the cause can be suggested in most cases by considering the character of the stool and the associated findings especially fever.

1. Bacterial gastroenteritis: The possibility of bacterial gastroenteritis is considerable when the fever is above 38.5°C and the diarrhea is severe or bloody. The main 5 causative organisms are shigella, salmonella, E. coli, campylobacter and yersinia enterocolitica. Other organisms as staphylococcus and pseudomonas may be responsible during massive antibiotic therapy. Cholera should be also considered in endemic areas. The stool character is a useful guide in suggesting the causative organism (see below). Accurate differentiation between these organisms can be only made by stool culture. Leucocytosis and elevated CRP level are common laboratory findings.

2. Viral gastroenteritis: Fever is usually below 38.5°C and the diarrhea is usually watery and not severe. The possibility is higher in the following situations (1) When there is preceding or associated viral respiratory infection, (2) When the diarrhea is occurring in winter season because viral gastroenteritis is the commonest cause of watery winter diarrhea. (3) When more than one member of the family are simultaneously affected. Rotavirus is by far the most common causative agent. Other viruses as enteroviruses (echo and coxsackieviruses) and adenovirus may be occasionally responsible.

3. Parasitic enteritis: Clinical manifestations depend on the causative agent. With ***Giardia lamblia infection,*** the diarrhea is usually watery, foul smelling, not severe and not associated with fever. The possibility becomes greater when diarrhea persists for more than 10 days (giardia is the most common cause of mild persistent watery diarrhea). With ***amoebiasis,*** diarrhea is commonly bloody but fever is absent (important differentiating point from bacterial gastroenteritis). Accurate diagnosis is made by stool analysis. Repeated stool analysis is important for the diagnosis of giardiasis because initial negative analysis does not exclude the possibility. It is important to remember that in parasitic enteritis, fever and vomiting are usually absent.

Diagnostic significance of the stool character in acute diarrhea

Acute watery diarrhea

E.coli (enterotoxinogenic form): The commonest cause of bacterial watery diarrhea.
Shigella (diarrheal form): High fever and abdominal cramps are common.
Chorea: Should be considered in endemic areas.
Staphylococcal: Uncommon, in patients with prolonged antibiotic therapy.
Viral (rotavirus): diarrhea is not severe, transient, mainly in winter.
Giardia lamblia: diarrhea is not severe, foul smelling, may persists, no fever.
Postenteritis malabsorption (sugar intolerance and/or milk allergy): Should be considered when watery diarrhea appears after initial improvement and re-feeding with milk (see below).

Acute bloody diarrhea

Shigella (dysenteric form): High fever and abdominal cramps are common. Diarrhea is frequent and mainly consisting of small amounts of blood and mucus.
Campylobacter: Watery and offensive for 2 - 3 days, then profuse bloody diarrhea.
E. coli (enteroinvasive form): Watery, then bloody diarrhea.
Salmonella and yersinia enterocolitica may be also the cause of bloody diarrhea.
Entamoeba histolytica: Diarrhea is usually not severe. No fever or vomiting.
Intussusception: It should be always excluded (see acute abdominal pain).

- **Stool analysis** is mainly useful for detection of parasites (giardia, entamoeba) and for documentation of presence of blood and mucus. It is also useful for diagnosis of sugar intolerance (low pH of the stool and present reducing substances).
- **Stool culture** is the only way for identification of the causative bacterial agent. Leukocytosis and elevated CRP level are common associated findings with bacterial gastroenteritis.
- **Electron microscopy of the stool and immunoassay** are the ways for diagnosis of rotavirus

4. What are the associated complications?

Five millions of children under the age of 5 years die every year with the complications of acute diarrhea. Most of these deaths occur in underdeveloped countries where nutritional deficiencies and environmental pollution are quite common and facilities for proper management are less available. These complications should be considered and excluded in every case of acute diarrhea.

Complications of acute gastroenteritis

1. Dehydration: Depressed fontanel, sunken eyes, dry tongue, lost skin turgor, weight loss.
2. Shock: Poor peripheral perfusion (cold extremities, skin mottling), tachycardia, hypotension.
3. Acute renal failure: Severe oliguria or anuria, acidotic breathing.
4. Metabolic acidosis: Acidotic breathing (deep rapid respiration), altered consciousness.
5. Hypokalemia: Abdominal distention (due to paralytic ileus) is the main feature.
6. Hypocalcemia: Convulsions or tetany.
7. Convulsions: Febrile, toxic, metabolic or intracranial hemorrhage (but not CNS infection).
8. Bleeding: DIC, hypoprothrombinemia, intussusception, renal vein thrombosis.
9. Persistent diarrhea: Persistent infection, malabsorption or fasting.
10. Malnutrition: Kwashiorkor (with one attack) and marasmus (with repeated attacks).

1. Dehydration: It is the most common and most serious complication and the main cause of death in fatal cases. It occurs mainly in infants with severe gastroenteritis due to severe diarrhea *(diarrheal dehydration),* severe persistent vomiting *(fasting dehydration)* or both. Infants are more susceptible to dehydration because gastro-enteritis is much commoner and loss of extracellular fluids is much easier.

Water content and water distribution in infants compared to adults

	Water content	Water distribution		
		Cellular	Extracellular	Vascular
Infants	75 %	40 %	30 %	5 %
Adults	60 %	40 %	15 %	5 %

• Extracellular fluid is 30% of body weight in infants compared to 15 % in adults.

Clinical signs of dehydration are: depressed fontanel, sunken eyes, dry tongue, lost skin turgor (or elasticity) over the abdomen, and acute weight loss. Diagnosis should also include the degree and the type of dehydration.

a) Degree of dehydration: Dehydration is assessed clinically as mild, moderate or severe according to the severity of signs and the degree of weight loss.

- Mild dehydration: 4% weight loss.
- Moderate dehydration: 8% weight loss.
- Severe dehydration: 12% weight loss.
- Weight loss above 15% is rapidly fatal.

Unfortunately, this accurate method cannot be applied in most cases because the accurate weight before illness is usually unknown. However, accurate weighing of the patient is very important because weight gain is the most reliable sign of effective rehydration.

b) Type of dehydration: Dehydration can be isonatremic, hypernatremic or hyponatremic according to the level of serum sodium:

(i) Isonatremic dehydration is the commonest type (75% of cases). It occurs when water and electrolyte losses are proportionate. Clinically, the tongue is dry and the skin turgor is lost to the same extent. Serum sodium level is normal (135 - 140 mEq/liter).

(ii) Hypernatremic dehydration is the next common (15% of cases) and the most serious type because convulsions and brain damage may occur. It is characterized by marked water loss (tongue is very dry and skin turgor is near normal). Serum sodium level is elevated (above 150 mEq/liter).

(iii) Hyponatremic dehydration is the least common (10% of cases) It is characterized by marked electrolyte losses (tongue is moist with marked loss of skin turgor). Serum sodium level is low (below 130 mEq/liter).

Types of dehydration

	Isonatremic (isotonic)	Hypernatremic (hypertonic)	Hyponatremic (hypotonic)
Incidence	75 %	15 %	10 %
Water/electrolyte losses	Water loss + + Na loss + +	Water loss + + + Na loss +	Water loss + Na loss + + +
Tongue	Dry	Very dry	Moist
Skin turgor	Lost	Normal	Marked loss
Consciousness	Lethargy	Irritability	Coma
Serum sodium	Normal (135-140 mEq/liter)	High (above 150 mEq/liter)	Low (below 130 mEq/liter)

2. Shock: Hypovolemic shock (due to dehydration) and/or septic shock (due to gram-negative septicemia) are common complication of severe bacterial gastroenteritis. Clinically, poor peripheral perfusion (cold extremities and skin mottling), tachycardia and hypotension are evident.

3. Acute renal failure: Severe gastroenteritis is the commonest cause of acute renal failure in infants. With severe dehydration, functional (prerenal) failure occurs. Organic (renal) failure occurs in persistent cases due to tubular damage. Clinically, severe oliguria (urine flow less than 1 ml/kg/hour) or anuria and acidotic breathing are the main manifestations. With clinical suspicion, diagnosis is confirmed by evaluation of renal function (elevated blood urea and creatinine levels).

4. Metabolic acidosis: It occurs due to severe diarrhea (loss of alkalies) and severe dehydration (renal failure). The main clinical manifestation is the deep rapid respiration (acidotic breathing). In severe cases, altered consciousness becomes evident. Diagnosis is confirmed by blood gas analysis. The severity can be determined by the degree of lowering of pH and serum bicarbonate level (see respiratory distress).

5. Hypokalemia: It is a common complication of severe diarrhea and dehydration. Abdominal distension is the main clinical manifestation. Serum potassium level is below 3.5 mEq/liter (normal level is 4 - 5.5 mEq/liter).

6. Hypocalcemia: It may occur with severe hypernatremic dehydration. Convulsions or tetany are the main manifestations. Blood calcium level is below 7 mg/dl (normal level is 9 - 11 mg/dl).

7. Convulsions: It is not due to CNS infection. The main causes are febrile convulsions (high fever), toxic convulsions (shigella, salmonella), metabolic convulsions (hypernatremia, severe hyponatremia, hypocalcemia) and intracranial hemorrhage (with disseminated intravascular coagulation).

8. Bleeding: Different types of bleeding may occur especially with severe complicated cases of bacterial gastroenteritis.

a) Disseminated intravascular coagulation (DIC): Shock, acidosis and gram-negative septicemia are the main precipitating factors (severe gastroenteritis is an ideal situation for DIC to develop). Bleeding from puncture sites and/or necrotic skin patches are the main clinical features. Internal hemorrhage especially intracranial hemorrhage is the most serious complication and it may be the cause of death in fatal cases. The main laboratory findings are thrombocytopenia, prolonged thrombin and prothrombin times and presence of the fibrin degradation products (FDPs).

b) Hypoprothrombinemia: Vitamin K deficiency and hypoprothrombinemia may occur in case of prolonged fasting (decreased vitamin K intake) or in those receiving oral antibiotic therapy (decreased intestinal synthesis of vitamin K). The main clinical presentation is bleeding from puncture sites. Prolonged prothrombin time is the only laboratory finding.

c) Intussusception: It may complicate severe cases of gastroenteritis. The possibility should be always considered in every case of bloody diarrhea. Paroxysmal abdominal pain and persistent vomiting are common associated findings (see acute abdominal pain and bleeding per rectum).

d) Renal vein thrombosis: Severe dehydration may predispose to unilateral or bilateral renal vein thrombosis. The main clinical manifestations are gross hematuria and flank mass (see hematuria and renal failure).

9. Persistent diarrhea: The natural course (duration) of diarrhea in acute gastroenteritis is 3-10 days. Persistence of diarrhea for more than two weeks or reappearance after initial improvement should suggest the following possibilities:

a) Persistent infection: Persistent diarrhea which has no relation to feeding should suggest persistent parasitic (giardia lamblia or entamoeba histolytica) or bacterial infection (shigella, salmonella or campylobacter). Repeated stool analysis (for parasites) and stool culture (for bacteria) are important for diagnosis. Giardiasis is the most common cause of persistent mild to moderate watery diarrhea (see above).

b) Postenteritis malabsorption: Transient malabsorption due to mucosal injury and damage of intestinal villi is a common complication of severe gastroenteritis. The main clinical manifestation is severe watery diarrhea that appears on refeeding with milk (refeeding diarrhea). The diarrhea usually subsides within 1 - 2 days of milk withdrawal and reappears again on refeeding with milk. The main 2 causes are:

(i) Sugar intolerence (carbohydrate malabsorption): Lactose intolerance due to lactase deficiency is the most common. However, other disaccharide intolerance (as sucrase intolerance) or monosaccharide intolerance (glucose-galactose intolerance) may also occur. Diagnosis is confirmed by the presence of acidic stool (pH below 5) that contains a sugar (stool examination for pH and reducing substance is important).

(ii) Cow's milk allergy (protein malabsorption): When watery diarrhea occurs on re-feeding with cow's milk, the possibility of cow's milk allergy should be considered. Therapeutic withdrawal of the cow's milk results in a rapid improvement.

(iii) Both conditions (sugar intolerance and milk allergy) may coexist.

Diagnostic significance of refeeding diarrhea in relation to the given food

Diarrhea on refeeding with breast milk: Lactose intolerance.
Diarrhea on refeeding with cow's milk: Lactose intolerance or milk allergy.
Diarrhea on refeeding with sucrose containing formula (as Isomil or Nursoy): Sucrose intolerance.
Diarrhea even with glucose or rice preparations: Glucose-galactose intolerance.

In most cases, the malabsorption is transient and persists for 1-2 weeks until regeneration of intestinal mucosa and villi takes place. During this period, the use of one of the hypoallergic-lactose free formulas is usually effective in most cases.

c) Fasting diarrhea: Prolonged restriction of milk may lead to fasting diarrhea, which is characteristically greenish and sticky. Immediate refeeding is indicated.

10. Malnutrition: Severe complicated gastroenteritis with prolonged dietary restriction may lead to kwashiorkor. Frequent repeated attacks may lead to growth failure and marasmus.

Possible investigations in severe cases of gastroenteritis

Stool analysis: For detection of parasites, blood and mucus.
Stool culture: For detection of the causative bacterial agent.
Stool pH and reducing substance: With suspected carbohydrate malabsorption.
CBC and CRP: Leukocytosis and elevated CRP are common with bacterial gastroenteritis.
Serum electrolytes: Sodium (type of dehydration), potassium and calcium (low levels).
Blood gases: For diagnosis of metabolic acidosis.
Blood urea and creatinine: With suspected renal failure.
Platelets, prothrombin time and fibrin degradation products (FDPs): With suspected DIC.
Abdominal x-ray and surgical consultation: With suspected intussusception.

B) CHRONIC DIARRHEA

Chronic diarrhea is a diarrhea that persists for more than 2 - 3 weeks. Chronic intestinal infections are by far the most common cause. Other causes as postenteritis malabsorption and other causes of malabsorption should be considered.

Causes of chronic diarrhea in infancy and childhood

Chronic infections: Parasitic, bacterial, tuberculous, immunodeficiency.
Postenteritis malabsorption: Sugar intolerance and cow's milk allergy.
Chronic nonspecific diarrhea: With excess intake of fruit juices, carbonated fluids or low fat diet
Other causes of malabsorption
Common causes: Biliary atresia, cystic fibrosis, celiac disease, massive resection
Rare causes: Abetalipoproteinemia, acrodermatitis enteropathica, inflammatory bowel diseases, intestinal lymphangiectasia, tumours, chronic pancreatitis, chronic biliary obstruction.

Precise diagnosis requires history taking, examination and some investigations.

Diagnostic approach in chronic diarrhea

History
Dietetic history: Useful in sugar intolerance, excess fruit juices, milk allergy and celiac disease.
Family history: May be positive in cystic fibrosis or immunodeficiency.
History of chronic chest disease: Cystic fibrosis, tuberculosis, immunoglobulin A deficiency.

Examination
Inspection of the stool: Useful for documentation of diarrhea, detection of blood.
Growth assessment: Growth failure documents the chronic nature of illness.
Jaundice: Biliary atresia or other causes of biliary obstruction.
Dermatitis of extremities and around body orifices: Acrodermatitis enteropathica.
Chronic chest disease: Cystic fibrosis, tuberculosis, immunoglobulin A deficiency.
Abdominal mass: Lymphoma, neuroblastoma, Crohn disease.
Ascites: Tuberculous peritonitis, lymphoma, intestinal lymphangiectasia.

Investigations
Stool analysis: For parasites (giardia, entamoeba, bilharzia ova).
For sugar intolerance (low pH and high sugar content).
For fat malabsorption (microscopic examination for fat cells).
For bloody diarrhea: Necrotizing enterocolitis, milk allergy (in infancy)
Ulcerative colitis, bilharzial colitis (in chilhood).
Stool culture: For bacteria (salmonella, shigella, campylobacter, yersinia enterocolitica).
Blood picture: Chronic anemia (malabsorption) or acanthocytosis (abetalipoproteinemia).
Sweat chloride test: With suspected cystic fibrosis.
Tuberculin test and chest x-ray: With suspected tuberculous enteritis.
Immunoglobulin levels: With suspected immunodeficiency.
Endoscopic studies of small bowel and mucosal biopsy: With suspected celiac disease.
Barium enema, colonoscopy and colonic biopsy: With suspected inflammatory bowel diseases.

1. Chronic infections: Chronic intestinal infections are by far the most common cause of chronic diarrhea: *chronic giardiasis* is the most common cause of persistent watery diarrhea. *Chronic amoebiasis* is also a common cause. *Chronic bacterial infection* especially shigella, salmonella, campylobacter and yersinia enterocolitica may be also responsible. *Bilharzial colitis* should be considered in rural endemic areas. *Tuberculous enteritis* should be considered when the chronic diarrhea is associated with fever, weight loss and edema of lower limbs. Ascites due to tuberculous peritonitis is a common associated illness. *Immunodeficiency* whether inherited (hypogammaglobulinemia, selective Ig A deficiency) or acquired (protein calorie malnutrition and AIDS) should be considered in case of intractable severe infection.

2. Postenteritis malabsorption: It is a common cause of persistent diarrhea following severe gastroenteritis, which causes mucosal injury and damage of intestinal villi. The main clinical manifestation is severe watery diarrhea that appears on refeeding with milk (refeeding diarrhea). The diarrhea usually subsides within 1-2 days of milk withdrawal and reappears again on refeeding with milk.

a) Sugar intolerance (carbohydrate malasbsorption): *Lactose intolerance* due to lactase deficiency is the most common and it leads to diarrhea on refeeding with breast or cow's milk (lactose is the sugar of both breast and cow's milk). *Sucrose intolerance* may also occur and leads to diarrhea on refeeding with sucrose containing formulas (as Isomil). *Glucose-galactose intolerance* is a severe forms which leads to diarrhea with all formulas and even with glucose or rice preparations. Diagnosis is confirmed by the presence of acidic stool that contains high sugar content (stool examination for pH and reducing substance is important).

b) Milk protein allergy (protein malabsorption): *Cow's milk allergy* is characterized by watery diarrhea that appears on refeeding with cow's milk. Diagnosis is clinical and depends on the control of diarrhea on withdrawal of the offending protein and its reappearance on refeeding with the cow's milk (challenge test). *Soy protein allergy* may also occur and leads to diarrhea on refeeding with soy protein containing formula (as Isomil). Both sugar intolerance and milk allergy may coexist (see also persistent diarrhea in acute gastroenteritis).

3. Chronic nonspecific diarrhea: It is a common condition in children, which is mostly related to dietetic errors as excess fruit juices, excess carbonated fluids and low fat diet (history is important). Clinically, diarrhea is the only finding with normal nutritional status and normal weight. Stool examination has no fat.

4. Other causes of malabsorption: Fat malabsorption (steatorrhea) results from hepatic, pancreatic or intestinal causes. **Laboratory diagnosis of steatorrhea** can be made by both screening and quantitative tests:

1. Screening tests: Low serum carotine level below 50 microgram/dl (normal level = above 100 microgram/dl) and microscopic examination of the stool for fat cells.

2. Quantitative tests: Estimation of fecal fat content in 72-hours specimen. It is only indicated if screening tests give equivocal results.

a) Biliary atresia: It is the most common hepatic cause of malabsorption in early infancy. Progressive jaundice, hepatomegaly and pale stool are the main clinical features (see neonatal jaundice). Other causes of biliary obstruction as chronic hepatitis and obstruction of common bile duct should be considered in children with chronic jaundice and pale stool.

b) Cystic fibrosis: It is an autosomal recessive disease characterized by chronic pancreatic insufficiency (chronic malabsorption) and chronic chest disease. The illness may present in neonatal period with the picture of meconium ileus. The possibility should be considered in every case of chronic diarrhea especially when associated with recurrent or chronic chest disease. Diagnosis depends on 4 criteria (1) Positive family history of affected sibling, (2) Chronic chest disease, (3) Positive sweat chloride test (increased chloride content of the sweat) and (4) Pancreatic achylia (absent pancreatic enzyme activity especially tryptic activity in duodenal contents).

c) Celiac disease (gluten induced enteropathy): It is a disease in which the proximal small bowel mucosa is damaged by exposure to dietary gluten (mainly the gliadin). Diarrhea usually starts at the age of 6 - 12 months with the onset of introduction of foods containing wheat or rye to the infant's diet (cereals and bread). The stool is bulky, greasy, frothy and offensive. Anemia, growth failure, wasting and abdominal distention occur in untreated cases. Diagnosis depends on 4 criteria: (1) Suggestive clinical symptoms and signs. (2) Positive serologic markers (antigliadin antibodies, antiendomysial antibodies and anti-tissue transglutaminase antibodies). These markers are highly sensitive and specific. Tissue transglutaminase can also detect asymptomatic patients. (3) Therapeutic response within a week to a gluten-free diet (see Practical Pediatric Therapy) and (4) Characteristic mucosal biopsy (flat mucosa with villous atrophy). Screening tests for fat malabsorption are not helpful because they may be normal in affected children.

d) Massive resection (short bowel syndrome): Chronic diarrhea is a common finding after massive intestinal resection as in treatment of intestinal atresia.

e) Other causes: *Abetalipoproteinemia (acanthocytosis)* is characterized by chronic diarrhea in infancy and acanthocytes in the peripheral blood. *Acrodermatitis enteropathica* is a disorder of zinc metabolism characterized by chronic diarrhea in infancy and dermatitis of extremities and around body orifices (mouth and napkin area). *Intestinal lymphangiectasia* should be considered when chronic diarrhea is associated with edema and ascites (chylous ascites). *Tumors* as lymphoma and neuroblastoma may occasionally present with chronic diarrhea. *Inflammatory bowel diseases* (Crohn disease and ulcerative colitis) should be considered in late childhood and adolescence. In Crohn disease, appendicitis-like pains are the most prominent clinical manifestation. Abdominal mass (mainly in right iliac fossa) and perianal disease (ulcers, infections and fistula) are common. In ulcerative colitis, chronic bloody diarrhea is the main presentation. In both conditions, extraintestinal manifestations as arthritis, hepatitis or erythema nodosum may occur. Diagnosis can be made by radiological studies (barium enema), colonoscopy and colonic biopsy.

5. Constipation

Acute constipation	Chronic constipation
Acute infections	Dysfunctional chronic constipation
Painful perianal lesions	Congenital aganglionic megacolon
Acute intestinal obstruction	Other organic cause

Constipation is defined as "difficult infrequent passage of hard fecal matter". It may be temporary (acute) or persistent (chronic).

A) ACUTE CONSTIPATION

1. Acute infections: Acute febrile illnesses are usually associated with anorexia and constipation. The mechanism of constipation is obviously the decreased food intake. It is the commonest cause of acute constipation.

2. Painful perianal lesions: Inspection of napkin area and anus is essential because painful lesions as anal fissure or napkin dermatitis may be responsible. The mechanism is the voluntary withholding of defecation.

3. Acute intestinal obstruction: Absolute constipation with vomiting and abdominal distension should suggest the diagnosis (see also acute vomiting, acute abdominal pain and acute abdominal distention).

B) CHRONIC CONSTIPATION

1. Dysfunctional chronic constipation: It is the commonest cause of chronic constipation in children above the age of 2 years. History of neonatal straining and parental manipulations by enemas or suppositories are common. Recurrent abdominal pain is common and abdominal examination may reveal hard fecal masses but without distention. The stool is huge in amount and rectal examination reveals a cavernous rectum filled with feces. Growth is essentially normal with no evidence of any other illness.

2. Congenital aganglionic megacolon (Hirschsprung disease): The illness may present in neonatal period with delayed passage of meconium or acute intestinal obstruction. In infancy, there is failure to pass stool except with enemas. Rectal examination is characteristically followed by an explosive discharge of feces and gases. Growth is impaired, abdominal distention is common and repeated episodes of diarrhea and enterocolitis may occur. Diagnosis is confirmed by radiological studies and rectal biopsy. Treatment is surgical.

3. Other causes: Chronic constipation is common with mental retardation, undernutrition and chronic use of drugs especially iron preparations.

6. Gastrointestinal Bleeding

Hematemesis	Bleeding per rectum
Acute hematemesis	**Acute bleeding per rectum**
Swallowed blood	Acute bloody diarrhea
Esophagitis	Intussusception, volvulus
Acute gastric ulceration	Henoch-Schonlein vasculitis
Recurrent hematemesis	**Recurrent bleeding per rectum**
Esophageal varices	Chronic bloody diarrhea
Peptic ulcer	Focal gastrointestinal lesions

Gastrointestinal bleeding is a common problem in pediatric practice. According to the site of external loss, bleeding can be classified into hematemesis and bleeding per rectum. Although most cases are due to local gastrointestinal lesions, ***blood diseases*** (purpuras and coagulation defects) should be routinely excluded especially when bleeding from other orificies (epistaxis, hematuria) and/or cutaneous manifestations (purpura, bruises) are also present.

A) HEMATEMESIS

Hematemesis (or vomiting of blood) occurs with swallowed blood or when bleeding originates from the esophagus, stomach or duodenum. ***Clinical assessment of the amount of blood loss*** is important and it depends on:

1. *Colour of blood:* Darkened altered blood (coffee ground) usually indicates a mild to moderate bleeding while fresh red blood is usually associated with massive bleeding. Coffee ground colour results from the effect of the gastric juice on the blood.

2. *Effect of bleeding:* Mild to moderate bleeding is usually not associated with hematological or cardiovascular effects. Massive bleeding is associated with acute anemia (intense pallor) and may be hypovolemic shock.

1. Acute hematemesis: ***Swallowed blood*** from the nose (epistaxis) or the oral cavity (bleeding gums) is probably the commonest cause of occasional nonrecurrent hematemesis. Careful history and examination of the nose and oral cavity are important. ***Esophagitis*** may be responsible and it is usually associated with severe dysphagia. ***Acute gastric ulceration*** may occur in critically sick patients as those with severe gastroenteritis and dehydration, septicemia, shock, burns and head trauma and leads to coffee ground vomiting. The condition may also follow ingestion of drugs as aspirin.

2. Recurrent hematemesis: ***Esophageal varices*** secondary to portal hypertension is the most important cause of spontaneous massive hematemesis. Abdominal examination is important for the clinical diagnosis of portal hypertension and it may reveal splenomegaly, hepatomegaly or hepatosplenomegaly. Ascites is a sign of advanced

disease. Endoscopic examination of the lower esophagus is essential for diagnosis of varices. ***Peptic ulcer*** should be considered when abdominal examination does not reveal enlarged organs or ascites. History of vomiting after feeding, poor appetite and epigastric pain are common. Abdominal examination may reveal epigastric tenderness. Endoscopic examination of the stomach and duodenum is essential for diagnosis.

B) BLEEDING PER RECTUM

Bleeding per rectum is a common form of gastrointestinal hemorrhage. The color of blood may provide a diagnostic clue to the site of bleeding. Passage of fresh bright red blood ***(hematochezia)*** usually indicates that the site of bleeding is below the distal ileum. However, massive hemorrhage above the distal ileum may also lead to hematochezia. Passage of blackened tarry stool ***(melena)*** indicates an origin above the distal ileum but it may also accompany hematemesis or lesions in the esophagus and stomach.

1. Acute bleeding per rectum: ***Acute bloody diarrhea*** is by far the most common cause of bleeding per rectum. The condition can be bacterial (shigella, salmonella, E. coli, campylobacter or yersenia enterocolitica) or parasitic (amoebic dysentery). With bacterial enteritis, high fever and vomiting are common associated findings while with amoebic dysentery these findings are usually absent. Diagnosis of acute bloody diarrhea is clinical and can be confirmed by stool analysis and stool culture (see acute diarrhea). ***Intussusception*** should be always considered and excluded especially in infants around the age of 6 months. It is characterized by sudden onset of paroxysmal severe abdominal pain, vomiting and passage of stool containing blood and mucus (red currant jelly stool). Abdominal examination may reveal an abdominal mass in the right upper quadrant. Rectal examination is essential and the finger is usually withdrawn covered with blood and mucus. It should be remembered that intussusception may also occur as a complication of gastroenteritis, so presence of diarrhea does not necessarily mean an acute infection (see also acute abdominal pain). Other surgical emergencies as ***volvulus*** may also lead to bleeding per rectum but this is usually a late finding (early manifestations are vomiting, abdominal pain and abdominal distension). ***Henoch-Schonlein vasculitis*** may lead to acute abdominal pain and bleeding per rectum. Diagnosis is readily made by the characteristic purpuric rash involving the buttocks and back of lower limbs (see also purpura and arthritis).

2. Recurrent bleeding per rectum: ***Chronic bloody diarrhea*** in infancy is usually caused by *milk allergy* or *necrotizing enterocolitis* secondary to severe bacterial infection. *Ulcerative colitis* should be considered in late childhood and adolescence and *bilharzial colitis* in rural endemic areas (see chronic diarrhea). ***Focal gastrointestinal lesions*** are the main cause of chronic or recurrent bleeding per rectum. *Anal fissure* is one of the most frequent causes. Constipation is an important predisposing factor. Pain on defecation and refusal to defecate are important symptoms. The blood is bright red and present on the surface of the hard stool. Diagnosis is made by inspection of the anal area during straining. *Rectal polyp* is also an important cause of recurrent, but painless bleeding. *Meckel diverticulum* is present in 3% of people and it may cause recurrent

painless bleeding per rectum especially during the first 2 years. Infections in the diverticulum may occur and lead to abdominal pain and volvulus may occur when intestinal loops turn around the band attached to the diverticulum. The diverticulum cannot be demonstrated by barium studies and preoperative diagnosis can be only made by technetium scanning. Diagnosis is usually made at operation in case of surgical emergencies as acute abdomen or acute intestinal obstruction. Other focal lesions as *hemangioma, intestinal polyposis or arteriovenous malformations* should be considered in recurrent unexplained bleeding per rectum. *Upper gastrointestinal causes* as esophageal varices and peptic ulcer should be also considered.

Causes and investigations of unexplained recurrent bleeding per rectum

Causes
- Rectal polyp
- Meckel diverticulum
- Intestinal hemangioma
- Intestinal polyposis
- Arteriovenous malformations
- Upper gastrointestinal lesions (varices, peptic ulcer)

Investigations
- Barium enema
- Endoscopic examination
  - Upper: Esophagus, stomach
  - Lower: Colon
- Technetium scanning
- Arteriography during bleeding
- Laparotomy (in severe cases)

• In up to 30% of cases, the cause remains unknown.

7. Abdominal Enlargement

Abdominal distention	Abdominal masses	Ascites
Acute abdominal distention	**Acute abdominal masses**	**Neonates**
Intestinal obstruction	Intussusception	Obstructive uropathy
Mechanical obstruction	Fecal masses	Chylous ascites
Functional obstruction	Distended bladder	Bilious ascites
Transient malabsorption	**Chronic abdominal masses**	Peritonitis
Chronic abdominal distention	Hepatosplenomegaly	With generalized edema
Megacolon	Renal and suprarenal masses	**Infants and children**
Mechanical	Other abdominal masses	Hypoproteinemia
Functional	Pancreatic	Portal hypertension
Chronic malabsorption	Intestinal	Local peritoneal causes
	Retroperitoneal	

Weak abdominal muscles as in rickets and malnutrition is sometimes the cause of large abdomen

Abdominal enlargement or "large abdomen" is a common clinical presentation in pediatric practice. According to the mechanism, it can result from:

1. Abdominal distention (due to distention of intestinal loops or colon by gases).
2. Abdominal masses (due to enlarged organs or other masses).
3. Ascites (due to accumulation of free fluid in the peritoneal cavity).
4. Weak abdominal muscles.

Differentiation between these entities can be clinically made by abdominal examination. By palpation, enlarged organs or other masses can be felt and by percussion, differentiation between abdominal distention (hyperresonance) and ascites (shifting dullness) is not difficult. Clinical diagnosis can be confirmed by abdominal x-ray (with distention), abdominal ultrasonography (with abdominal masses) and diagnostic abdominal paracentesis (with ascites).

A) ABDOMINAL DISTENTION

Abdominal distension can be acute or chronic and can be caused by intestinal obstruction or malabsorption. Presence of constipation or diarrhea is an important differentiating point.

1. Acute abdominal distention: ***Acute intestinal obstruction*** should be considered when the acute distention is associated with vomiting and constipation. Urgent plain x-ray on the abdomen (erect position) is important to demonstrate the multiple air-fluid levels. Acute intestinal obstruction can be mechanical (organic) or functional (paralytic ileus). With *mechanical obstruction,* severe colicky abdominal pain is usually present and bowel sounds are also present while with *paralytic ileus*, the

abdominal pain is minimal or absent and bowel sounds are also absent. Diagnosis of the cause depends on the associated findings. ***Transient malabsorption*** should be considered when abdominal distention is occurring with or following severe gastroenteritis. Sugar intolerance and milk protein allergy are the two main causes. Abdominal distention and watery diarrhea usually follow ingestion of the offending food.

Acquired intestinal obstruction

	Mechanical obstruction	Paralytic ileus
Main features	Severe colicky abdominal pain Present bowel sounds	Minimal or absent abdominal pain Absent bowel sounds
Causes	Incarcerated inguinal hernia Intussusception Meckel diverticulum and volvulus Fecal or round worm masses Peritonitis Postoperative adhesions Other causes (tumors, cysts)	Pneumonia Gastroenteritis (toxic ileus) Hypokalemia Uremia Peritonitis Postoperative ileus

• Distention with gastroenteritis can be due to toxic ileus, hypokalemia or transient malabsorption.

2. Chronic abdominal distention: ***Megacolon*** (marked colonic distension) occurs with chronic constipation whether functional (Hirschsprung disease) or mechanical (anorectal stenosis). Chronic dysfunctional constipation can also lead to acquired megacolon. Barium enema can demonstrate the marked colonic distention. ***Chronic malabsorption*** with chronic diarrhea can also cause chronic distension.

B) ABDOMINAL MASSES

Abdominal masses can be acute or chronic. Acute masses are usually symptomatic and usually accompanied with acute abdominal pain. Chronic masses, on the other hand, are usually silent and are accidentally discovered by parents or during routine abdominal examination. Huge abdominal masses often lead to abdominal enlargement.

1. Acute abdominal masses: Acute abdominal pain is usually the main presentation. Other clinical manifestations depend on the cause:

a) Intussusception: Severe paroxysmal abdominal pain, vomiting and red currant jelly stool in an infant around the age of 6 months is the main presentation. Abdominal examination reveals a sausage shaped mass mainly in the right upper quadrant in 70% of cases. With rectal examination, the finger is withdrawn covered with blood and mucus.

b) Fecal masses: Acute abdominal pain and acute constipation are the main presenting features. Abdominal examination reveals one or more sausage shaped masses mainly felt in the left lower quadrant.

c) Distended bladder: Acute abdominal pain and history of urinary retention are usually present. Abdominal examination reveals a globular midline suprapubic mass. Firm pressure on the mass may lead to immediate urination. Uretheral obstruction or autonomic disturbance (as with acute spinal cord disease) are the main causes.

2. Chronic abdominal masses: These masses are either accidentally discovered or suspected in patients with abdominal enlargement.

a) Hepatosplenomegaly: Enlargement of the liver, spleen or both organs is the commonest cause of abdominal masses. Diagnosis of the cause of enlargement depends on the age of the patient, the predominant enlarged organ and the associated clinical manifestations (see hepatic and splenic enlargement).

(b) Renal and suprarenal masses: The most common and most serious masses are neuroblastoma and Wilms tumor. Other renal masses whether unilateral or bilateral should be also considered.

(i) Neuroblastoma: It is a common malignant tumor mostly seen below the age of 5 years. The mass is usually present in the right or left upper quadrant. It is usually hard with irregular or nodular surface and commonly crosses the middle line. Other manifestations as hepatomegaly, proptosis, subcutaneous nodules, anemia or bony pains may be also present. Bone marrow examination reveals neuroblastoma cells in 70% of cases (see common malignancies).

(ii) Wilms tumor: It is a common malignant tumor in young children (around the age of 3 years). The mass is usually present in the right or left upper quadrant. It is usually firm with a smooth surface and usually does not cross the middle line. Other manifestations as hematuria may be also present (see common malignancies).

(iii) Other renal masses: Hydronephrosis, cystic dysplasia, renal artery or renal vein thrombosis may cause unilateral or bilateral renal masses. Other clinical manifestations as hematuria or manifestations of chronic renal failure may be also present.

c) Other abdominal masses: Abdominal masses may arise from the pancreas, intestine or retroperitoneal tissues. In females, ovarian, uterine and vaginal masses should be also considered.

(i) Pancreatic masses: Pancreatic pseudocyst is the commonest pancreatic mass. The mass is epigastric and history of blunt trauma to the abdomen is usually obtained. Other pancreatic cysts as retention cyst and cystadenoma are less common.

(ii) Intestinal masses: Masses originating from the gut usually present with a mobile midabdominal mass. Intestinal cysts (mesenteric cyst, omental cyst, duplication cyst) and intestinal lymphoma are the main causes. With intestinal lymphoma, the mass may be huge and ascites may be also present (huge abdominal mass with ascites is due to intestinal lymphoma until proved otherwise). Inflammatory masses as with tuberculous mesenteric ademtis or with Crohn disease (regional enteritis) are uncommon.

(iii) Retroperitoneal masses: Teratoma, rhabdomyosarcoma, fibrosarcoma or lymphoma may arise from the retroperitoneal tissue and present with a fixed abdominal mass in the upper or lower abdomen.

iv) ***Masses in females:*** Ovarian cysts and tumors should be considered in females with a lower abdominal mass. Uterine causes (tumors, hydrometria, hematometria) and vaginal causes (tumors, hydrocolpos, hematocolpos) are less common.

Causes of cystic abdominal masses

Liver and gall bladder: Choledochal cyst and hepatic cysts (see hepatomegaly).
Spleen: Splenic cysts (see splenomegaly).
Kidneys: Hydronephrosis, cystic dysplasia (unilateral or bilateral).
Pancreas: Pancreatic pseudocyst, retention cyst, cystadenoma.
Intestine: Mesenteric cyst, omental cyst, duplication cyst.
Ovary: Ovarian simple cysts (follicular, leutin), cystadenoma, cystadenocarcinoma.
Uterus and vagina: Hydrometria, hematometria, hydrocolpos, hematocolpos.

Possible investigations of chronic abdominal masses

Abdominal ultrasonography: In all cases. It is the most essential investigation.
Intravenous pyelography (IVP): With renal masses especially hydronephrosis.
Arteriography and doppler ultrasonography: with suspected renal vascular disease.
Bone marrow examination: With suspected neuroblastoma or lymphoma.
Barium enema: With suspected Crohn disease (regional enteritis).
Evaluation of renal function: With bilateral renal masses.
Laparotomy and open biopsy: With suspected malignant tumor.

C) ASCITES

Ascites is the accumulation of free fluid in the peritoneal cavity. The ascitic fluid can be transudate, exudate, chylous, hemorrhagic, bilious or urine. Diagnostic abdominal paracentesis and examination of the ascitic fluid are essential for diagnosis.

Types of ascitic fluid

Transudate	Clear fluid, low specific gravity (below 1015), low proteins (below 2.5 gm/dl), few cells (mainly lymphocytes), no detected organisms.
Exudate	Turbid fluid, high specific gravity (above 1018), high proteins (above 3.0 gm/dl), many cells (lymphocytes, polymorphs). organisms may be detected.
Chylous	Milky fluid with large number of fat globules on microscopic examination.
Hemorrhagic	Bloody fluid with red cells on microscopic examination.
Bilious	Greenish fluid (bile).
Urinary	Yellowish fluid (urine).

Diagnosis of the cause of ascites depends on the age of the patient, associated clinical manifestations (edema, abdominal masses) and examination of the ascitic fluid.

(a) Ascites in neonatal period and early infancy

1. Obstructive uropathy with perforation: It is the commonest cause of neonatal ascites. The site of leakage may be difficult to locate. The ascitic fluid is *urine.*

2. Chylous ascites: Congenital lymphatic obstruction or occlusion may lead to chylous ascites in neonatal period or early infancy. The ascitic fluid is *chyle (lymph).*

3. Bilious ascites: Congenital malformations of the gall bladder may lead to jaundice, pale stool and ascites. The ascitic fluid is *bile.*

4. Peritonitis: Ascites in a critically sick neonate should raise the possibility of peritonitis. The main causes are perforation of a hollow viscus, gangrenous bowel, necrotizing enterocolitis and septicemia. The ascitic fluid is *exudate.*

5. Ascites with generalized edema: Severe Rh incompatibility, congestive heart failure and congenital nephrosis are the main causes. The ascitic fluid is *transudate.*

(b) Ascites in late infancy and childhood

1. Hypoproteinemia: Ascites with *generalized edema* is mostly due to hypoproteinemia. Nephrotic syndrome is by far the commonest cause. If urine examination does not reveal massive proteinuria, other causes of hypoproteinemia especially protein losing enteropathy and liver cell failure should be considered. With hypoproteinemia, serum proteins are low and the ascitic fluid is ***transudate.*** It is important to remember that ascites with generalized edema may occur without hypoproteinemia as in case of intestinal lymphangiectasia (ascitic fluid is chylous).

2. Portal hypertension: Ascites with *hepatomegaly, splenomegaly or hepatosplenomegaly* should suggest the diagnosis of portal hypertension. Other manifestations of portal hypertension as dilated abdominal wall veins and esophageal varices (with hematemesis) may be also present. The ascitic fluid is ***transudate.*** Ascites with splenomegaly should suggest a prehepatic cause (as portal vein thrombosis) while ascites with hepatomegaly or hepatosplenomegaly should suggest a hepatic or posthepatic cause.

Clinical manifestations of portal hypertension

Collateral circulation
- Esophageal varices: hematemesis.
- Caput medusa: Dilated abdominal wall veins around the umbilicus.

Organomegaly
- Splenomegaly: With prehepatic causes
- Hepatomegaly: With hepatic and posthepatic causes.
- Hepatosplenomegaly: With liver cirrhosis (hepatic causes).

Ascites (due to portal hypertension with or without hypoproteinemia)

- Diagnosis is confirmed by portal venography and Doppler ultrasonography.

Causes of portal hypertension

Prehepatic causes

Primary portal hypertension.

Portal or splenic vein obstruction: Idiopathic, umbilical catheterization, umbilical sepsis.

Hepatic causes

Presinusoidal causes (normal wedged hepatic venous pressure).

Congenital hepatic fibrosis, bilharzial fibrosis, hepatic infiltration.

Postsinusoidal causes (increased wedged hepatic venous pressure).

Liver cirrhosis, veno-occlusive disease, Budd-Chiari syndrome.

Posthepatic causes

Congestive heart failure Tricuspid valve disease Constrictive pericarditis	Cardiac examination is essential in every case of ascites. Echocardiography is also important.

- Important causes of liver cirrhosis are:
  - In infancy: Biliary atresia, galactosemia, tyrosinemia.
  - In childhood: Posthepatitic (following hepatitis), metabolic (Wilson disease).

Veno-occlusive disease is an intrahepatic obstruction of hepatic veins by thrombotic lesions, which results in a postsinusoidal portal hypertension. The cause is unknown, but ingestion of herbal hepatotoxins may be responsible. Clinical diagnosis depends on the presence of hepatomegaly, rapidly developing ascites and dilated abdominal wall veins in a malnourished child between the ages of 1- 4 years. Jaundice is usually mild or absent and spleen is not enlarged. The prognosis is generally bad as most cases deteriorate and die within several months of onset. Some cases may live longer and develop liver cirrhosis (chronic veno-occlusive disease). Ascitic fluid is a transudate but with a high protein content. Diagnosis is confirmed with liver biopsy, which reveals a centrilobular venous congestion and necrosis. Thrombosis of large hepatic veins appears on postmortem examination.

3. Local peritoneal causes: Ascites without generalized oedema or organomegaly (liver, spleen or both) is mostly due to a local peritoneal cause.

a) Peritonitis: *Acute peritonitis* should be considered in critically sick patients with high fever, abdominal pain and ascites. *Tuberculous peritonitis* is considered when history of weight loss and chronic diarrhea are also present. Edema of lower limbs due to protein losing enteropathy and hypoproteinemia is also common. The ascitic fluid is exudate.

b) Malignant ascites: Ascites with an abdominal mass should suggest lymphoma or neuroblastoma. The ascitic fluid may be hemorrhagic with malignant cells.

c) Chylous ascites: Lymphatic obstruction (as with intestinal lymphangiectasia) may lead to a chylous ascites. Edema (which may be generalized or asymmetric) and chronic diarrhea may be also present. The ascitic fluid is chyle.

8. Hepatic and Splenic Enlargement

Hepatomegaly	Splenomegaly	Hepatosplenomegaly
Acute liver diseases	**Infections**	**Newborns and young infants**
Acute hepatitis	Infectious mononucleosis	Neonatal hepatitis
Liver abscess	Typhoid fever	Biliary atresia
Acute CHF	Brucellosis	Metabolic liver disease
Acute veno-occlusive disease	Malaria	**Infants and young children**
Reye syndrome	Leishmaniasis (Kala-Azar)	Chronic hemolytic anemia
Chronic liver disease	**Chronic splenic disease**	Acute leukemia
Chronic hepatitis	Chronic infections	Metabolic disease
Chronic cholestasis	Portal hypertension	**Old children**
Chronic congestion	Chronic hemolytic anemia	Chronic hepatitis
Metabolic liver disease	Metabolic diseases	Bilharziasis
Liver tumours	Tumours	Wilson disease
Liver cysts	Splenic cysts	

Enlargement of the liver, spleen or both organs is a common presentation in pediatric practice. It is important to emphasize that in about 10% of normal infants and children, the liver and spleen can be palpated just below the costal margin. This normal finding should not be confused with the pathological enlargement where the lower border of the enlarged organ is considerably below the costal margin.

The enlargement can be measured in centimeters below the costal margin in midclavicular line or preferably the degree of enlargement can be assessed by the relation of the lower border to the abdominal areas.

Degrees of hepatic or splenic enlargement

Mild enlargement: Lower border is in the right or left hypochondrial area
Moderate enlargement: Lower border is reaching the right or left lumbar areas
Huge enlargement: Lower border is reaching the right or left iliac fossa

- **Abdominal ultrasonography** is very useful for:

1. Confirmation of the degree of enlargement (mild, moderate or huge).
2. Identification of the nature of enlargement (diffuse, focal or cystic).
3. Detection of associated findings as ascites or portal vein dilatation.
4. Guidance in procedures as percutaneous liver biopsy or drainage of an abscess.

Identification of the cause of enlargement requires consideration of the associated clinical manifestations in addition to some investigations.

A) HEPATOMEGALY

Isolated hepatomegaly (without splenic enlargement) is the most common clinical presentation of acute and chronic liver diseases. The hepatic enlargement occurs due to infection or inflammation, obstruction, vascular congestion, metabolic storage, tumors or cysts.

(a) Acute liver disease

With acute liver diseases, hepatomegaly is usually tender due to the rapid expansion of the hepatic capsule. Other clinical manifestations are commonly present especially fever, abdominal pain and jaundice. The major risk is acute hepatic failure (progressive jaundice, bleeding and rapidly developing coma), which is fatal in up to 70% of cases.

1. Acute hepatitis: It is a common potentially serious health problem, which can be caused by infectious or noninfectious causes. Viral hepatitis due to infection with hepatic viruses (5 types) is the most common cause but other infectious (viral, bacterial, parasitic) and noninfectious causes (toxic, metabolic) should be also considered.

Causes of acute hepatitis

Infective hepatitis
- Viral hepatitis: Hepatitis viruses (5 types), cytomegalovirus, Epstein-Barr virus.
- Bacterial hepatitis: With septicemia, miliary tuberculosis.
- Parasitic hepatitis: Malaria.

Toxic or drug-induced hepatitis
- Commonly used drugs: Erythromycin, isoniazid, paracetamol, salicylates.
- Other drugs: Chlorpromazine, antiepileptic drugs, antineoplastic drugs, androgens.

Metabolic hepatitis
- Acute ischemia: Shock, hypoxia, acute congestive heart failure.
- Metabolic disease: Wilson disease, galactosemia, tyrosinemia.

Diagnosis of acute hepatitis should include the clinical form, confirmatory investigations of acute liver injury and identification of the causative agent.

a) Clinical forms of acute hepatitis: There are four clinical forms or types:

(i) Icteric hepatitis: It is the most common form. Clinical manifestations can be divided into 3 stages (preicteric, icteric and convalescent stages). Preicteric stage is characterized by mild fever, anorexia, vomiting and abdominal pain. This stage usually lasts for 4 - 6 days and the urine usually becomes dark (bilirubinuria) during the last 1- 3 days. During the icteric stage, jaundice appears and the liver is enlarged and tender. The early manifestations as fever, vomiting and abdominal pain disappear but anorexia may continue. This stage usually lasts for 2- 4 weeks. However, it may be as short as one week or as long as several weeks. Convalescent stage starts with complete resolution of

hepatic injury. During this stage some children may continue to complain of malaise and fatigue for several weeks.

(ii) Cholestatic hepatitis: In some cases, obstruction to biliary flow occurs. In addition to jaundice, pruritis and clay-coloured stool are prominent.

(iii) Anicteric hepatitis: This form is commoner in infants. It is mainly characterized by gastrointestinal manifestations as vomiting, diarrhea, colics and anorexia. It is also called "asymptomatic hepatitis".

(iv) Fulminant hepatitis: It is the least common but the most serious form. Manifestations of acute hepatic failure occur (progressive jaundice, bleeding and rapidly developing coma) and mortality rate is high (around 70%).

b) Confirmatory investigations: Investigations to confirm the presence of acute liver injury include serum bilirubin level, liver enzymes (serum transferases), serum albumin and prothrombin time. Blood ammonia and serum electrolytes are also important.

Laboratory evidence of acute liver Injury

Direct or mixed hyperbilirubinemia

Mild (2-6 mg/dl), moderate (6-10 mg/dl), severe (more than 10 mg/dl).
In fulminant hepatitis, peak levels above 20 mg/dl occur.

Raised serum transferases

Raised serum aspartate aminotransferase (AST). Formerly known as (SGOT).
Raised serum alanine aminotransferase (ALT). Formerly known as (SGPT).
(Levels between hundreds and thousands are common).

Evidence of acute hepatic failure (in fulminant hepatitis)

Rising bilirubin level (above 10 mg/dl).
Low serum albumin level (below 3 gm/dl).
Prolonged prothrombin time (more than 20 seconds).
High blood ammonia level (above 150 mcg/dl).
Hypokalemia, hyponatremia and metabolic acidosis.

c) Identification of the causative agent: Viral hepatitis due to infection with hepatitis viruses (5 types) is by far the most common cause of acute hepatitis. *Hepatitis A* is the most common and it is transmitted through contaminated food or water. Incubation period is short (4 weeks), onset is acute and course is rather short. Fulminant hepatitis is rare and carrier state or chronic liver disease does not occur. *Hepatitis B* is the second most common and it is transmitted through transfusions. Incubation period is long (2 - 6 months), onset is insidious and course is prolonged. Fulminant hepatitis may occur and carrier state or chronic liver disease may also occur. *Hepatitis C* is similar to hepatitis B with the difference of being more insidious and more prolonged. *Hepatitis D* is also similar to hepatitis B and usually presents with fulminant hepatitis. *Hepatitis E* is similar to A with the difference of being rare below 15 years.

Laboratory identification of the causative agent of acute hepatitis

Hepatitis viruses markers

Hepatitis A: Anti-HAV IgM and IgG (IgM early and IgG few weeks later).

Hepatitis B: Hepatitis B surface antigen (HBsAg) and Anti-HBV antibodies.

* Hepatitis B surface antigen (HBsAg): It indicates infection with HBV but it cannot differentiate between acute and chronic infections (HBV antibodies are needed for differentiation).
* Anti-HBV antibodies especially: - Anti-HBc IgM: Most reliable single marker of acute infection.
  - Anti-HBc IgG: Past or chronic infection.

Hepatitis C, D and E: Serological tests are also available.

Other viruses

Epstein-Barr virus: Monospot test.

Cytomegalovirus: Serological tests.

Bacteria

Blood culture in patients with septicemia and acute hepatitis.

Parasites

Blood film for malaria.

Metabolic

Wilson disease: Serum ceruloplasmin level (especially with recurrent hepatitis).

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2. Liver abscess: The possibility of liver abscess (pyogenic or amoebic) should be considered in patients presenting with high fever and tender hepatomegaly. It should be also considered in the differential diagnosis of unexplained prolonged fever (see prolonged fever). Leukocytosis, high ESR and elevated transferases are usually present. Abdominal ultrasonography is essential for diagnosis and localization.

3. Acute congestive heart failure: The clinical triad of tachycardia, tachypnea and enlarged tender liver is diagnostic (see congestive heart failure).

4. Acute veno-occlusive disease: The clinical triad of hepatomegaly, dilated abdominal wall veins and rapidly developing ascites in a child between 1- 4 years is usually diagnostic (see also ascites).

5. Reye syndrome: It is a rare disease, which is also known as "acute encephalopathy with fatty infiltration of the liver". The possibility should be considered in patients presenting with altered consciousness and hepatomegaly. Jaundice is usually absent but vomiting and convulsions are common. Blood ammonia level and serum transferases are elevated. CSF examination is normal and CT scan of the head demonstrates a brain edema (see comatose child). The cause is unknown but viral infections (especially when aspirin is used) may be responsible.

(b) Chronic liver disease

With chronic liver diseases, hepatomegaly is usually not tender. Other clinical manifestations may or may not be present. The major complication is the development of liver cirrhosis, which eventually leads to chronic hepatic failure and portal hypertension.

Possible clinical findings in patients with chronic liver disease

Manifestations of chronic hepatic failure

General deterioration of health: Anorexia, weight loss, easy fatigability, and low-grade fever.
Jaundice: Chronic conjugated hyperbilirubinema.
Ascites: Due to hypoproteinemia and portal hypertension.
Bleeding: Due to coagulation defect, esophageal varices, hypersplenism (thrombocytopenia)
Fetor hepaticus: Fruity apple odor due to exhaled methyl mercaptan.
Cutaneous manifestations
- Edema of lower limbs: due to hypoproteinemia
- Plamar erythema: Erythema opposite heads of metacarpals, thenar and hypothenar areas
- Spider naevi: Dilated arterioles and capillaries in head, neck, upper limbs and chest.
- Clubbing of fingers: Especially with biliary cirrhosis.

Hepatorenal syndrome: Oliguria, urinary sodium loss, acid base disturbance.
Hepatic or portosystemic enoephalopathy: Precipitated by infections, bleeding or diuretics.
- Stage I: Insomnia, inversion of sleep rhythm.
- Stage II: Irritability, flapping tremors (repeated flexion and extension of hands).
- Stage III: Lethargy and confusion.
- Stage IV: Coma, convulsions.

Manifestations of portal hypertension

Collateral circulation: Dilated abdominal wall veins, esophageal varices.
Splenomegaly.
Ascites.

Manifestations suggesting a specific pathology or disease

Pale clay-coloured stool and pruritis: Chronic cholestasis.
Arthritis: Chronic active hepatitis, inflammatory bowel diseases.
Episodes of acute hemolysis: Wilson disease, chronic hemolytic anemia.
Chronic chest disease: Cystic fibrosis, alpha one antitrypsin deficiency.
Chronic heart disease: Posthepatic portal hypertension.
Chronic or recurrent neurological disease: Wilson disease.

Investigations in patients with chronic liver diseases have 3 objectives:

1. Assessment of functional integrity (liver function tests).
2. Assessment of structural integrity.
3. Specific tests for diagnosis of certain diseases.

Physiological classification of chronic liver disease

Compensated liver disease

Absent clinical and laboratory evidence of chronic hepatic failure

Decompensated liver disease

Present clinical and laboratory evidence of chronic hepatic failure. Patients with deep jaundice, massive ascites, very low albumin and prolonged prothrombin time have a poor prognosis.

Possible investigations in patients with chronic liver disease

Assessment of functional integrity (liver function tests)

Serum bilirubin level.
Serum transferases: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
Serum proteins and albumin/ globulin ratio.
Prothrombin time.
Other tests: Serum alkaline phosphatase, serum cholesterol, blood ammonia.

Assessment of structural Integrity

Abdominal ultrasonography: Diffuse, focal or cystic lesions.
Radiological procedures: CT scan, Magnetic resonance imaging (MRI).
Radio-isotopic scanning: Technetium scanning.
Liver biopsy: For histological and biochemical study.

Specific tests for diagnosis of certain diseases

Viral markers of hepatitis B, C and D and serology for other viruses (in chronic viral hepatitis).
Immunological tests (in chronic autoimmune hepatitis)
- Immunoglobulins
- Autoantibodies (Antinuclear, antimitochondrial, anti-smooth muscles) and Coombs test.

Tests for metabolic diseases (in metabolic hepatitis)
- Serum ceruloplasmin, serum copper and urinary copper (Wilson disease).
- Alpha one antitrypsin level (alpha one antitrypsin deficiency).
- Tests for galactosemia and tyrosinemia.
- Sweat chloride test and pancreatic enzyme activity (cystic fibrosis).

Other tests
- Nonspecific and specific test for chronic hemolytic anemias.
- Alpha feto-protein: High in tyrosinemia and hepatic tumors.
- Stool and urine examination for bilharzial ova (in suspected bilharziasis).

1. Chronic hepatitis: It is a chronic liver inflammation persisting for 6 months or more. Chronic viral infection is the most common but other causes as autoimmune hepatitis, metabolic hepatitis and drug-induced hepatitis should be in mind.

Causes of chronic hepatitis

Chronic viral hepatitis

Hepatitis B, Hepatitis C and Hepatitis D

Chronic autoimmune hepatitis

Isolated disease.
With other diseases (as systemic lupus eryhtematosus and inflammatory bowel diseases).

Chronic metabolic hepatitis

Wilson disease.
Alpha one antitrypsin deficiency.
Galactosemia and tyrosinemia.
Cystic fibrosis, Neimann-Pick disease type 2 and glycogenosis type 4.

Drug-induced hepatitis

Antituberculous drugs as isoniazid and rifampicin.

a) Chronic persistent hepatitis: It is a benign illness that usually follows infection with hepatitis B or C viruses and fails to resolve within 6 months. Anorexia, easy fatigability, mild jaundice and mild hepatomegaly are the main clinical findings. Mild elevation of serum bilirubin and serum aminotransferases is usually present. Laboratory manifestations of severe hepatic disease as low albumin level and prolonged prothrombin time are absent. Prognosis is good and recovery occurs in all cases.

b) Chronic active hepatitis: It is a serious progressive form, which may follow infections with hepatitis B, C or D viruses or other types of chronic hepatitis as autoimmune hepatitis and metabolic hepatitis. Clinically, anorexia, easy fatigability, vomiting, moderate jaundice and tender hepatomegaly are usually present. Laboratory findings include moderate to severe elevation of serum bilirubin and aminotransferases. Manifestations of severe hepatic disease as low albumin level and prolonged prothrombin time may be present. In autoimmune cases, abnormal immune reactions can be detected (see above). Diagnosis is made by liver biopsy, which reveals a marked piecemeal necrosis of liver cells with disturbed lobular pattern. Liver cirrhosis and progressive liver cell failure are the major complications.

2. Chronic cholestasis: Persistent conjugated hyperbilirubinemia with pale clay-colored stool and pruritis should suggest chronic cholestasis due to intrahepatic or extrahepatic obstruction to bile flow. Xanthomas (due to retained lipids) and rickets (due to malabsorption) may occur in chronic cases. Laboratory findings include conjugated hyperbilirubinemia, high alkaline phosphatase and hypercholesterolemia.

Causes of chronic cholestasis

Extrahepatic obstruction

- Extrahepatic biliary atresia.
- Obstruction to common bile duct (choledochal cyst, stone, lymph nodes, tumors).
- Duodenal atresia, tumours of the head of pancreas.

Intrahepatic obstruction

- Cholestatic hepatitis.
- Primary biliary cirrhosis.
- Familial cholestasis (benign recurrent, Dubin Johnson and Rotors syndromes).

- Abdominal ultrasonography, radiological studies, radio-isotopic scanning and may be liver biopsy are needed for identification of the cause.

3. Chronic hepatic congestion: Chronic congestive hepatomegaly occurs with conditions causing posthepatic portal hypertension as chronic congestive heart failure, tricuspid valve disease, constrictive pericarditis, high superior vena caval thrombosis, Budd-Chiari syndrome and chronic veno-occlusive disease.

4. Metabolic liver disease: Hepatomegaly with or without jaundice is the most common clinical presentation of metabolic liver diseases. Other clinical manifestations depend on the causative disease. Liver biopsy with histological and biochemical studies is the most reliable diagnostic procedure.

Causes of metabolic liver disease

Carbohydrates : Galactosemia, glycogen storage diseases.
Aminoacids Tyrosinemia, argininemia, argininosuccinic acidemia.
Lipids : Gaucher disease, Niemann Pick disease, other lipidoses.
Minerals : Wilson disease, Hemochromatosis, porphyria.
Bilirubin : Crigler-Najjar syndrome, Gilbert disease.
Others : Cystic fibrosis, alpha one antitrypsin deficiency.

Wilson disease is the mainly treatable metabolic liver disease and it should be considered in children above 8 years with recurrent or chronic hepatitis. It should be also considered in those presenting with recent neurological disease or acute hemolytic anemia. It is also a good possibility when acute hepatitis and acute hemolytic anemia coexist. Diagnosis depends on:

1. Low serum ceruloplasmin level below 20 mg/dl (normal level is 30 - 60 mg/dl).
2. High serum copper level above 200 mcg/dl (normal level is 50 - 150 mcg/dl).
3. High urinary copper excretion more than 100 mcg/day (normally, below 40 mcg/day).
4. High hepatic copper content with liver biopsy (more than 250 mcg/gm dry weight).

5. Liver tumors: Tumors of the liver can be primary or secondary. *Metastatic secondary tumors* are by far the most common. Neuroblastoma should be considered in infants presenting with huge hepatomegaly. The primary tumor of neuroblastoma may be small and liver metastasis is sometimes is only presentation. *Other secondary tumors* as Wilms tumor, leukemia, lymphoma and histiocytosis should be also considered. *Primary liver tumors* are rare. Benign tumors (as infantile hemangio-endothelioma) and malignant tumors (hepatoblastoma and hepatoma) are the main causes. Alpha feto-protein is increased with primary malignant tumors. Abdominal ultrasonography, radiological studies and liver biopsy are essential for diagnosis.

Liver tumors

Secondary liver tumors
Solid: Neuroblastoma, Wilms tumor, carcinoma of pancreas.
Diffuse: Leukemia, lymphoma, histiocytosis.

Primary liver tumors
Benign: Infantile hemangioendothelioma, adenoma, teratoma, hamartoma.
Malignant: Hepatoblastoma, hepatoma, sarcoma.

6. Liver cysts: Cysts of the liver are mostly caused by congenital malformations of the liver or biliary system. Acquired cysts whether parasitic (hydatic cyst) or neoplastic (teratoma, cystadenoma) should be also considered. Congenital cysts may be asymptomatic or may present with hepatomegaly, cholestasis or portal hypertension. Abdominal ultrasonography and radiological studies are essential for diagnosis. Liver biopsy and histological study are also needed for accurate diagnosis.

Congenital cysts of the liver and biliary system

Choledochal cyst: Cystic dilatation of the common bile duct.
Caroli disease: Cystic dilatation of the intrahepatic bile ducts.
Congenital hepatic fibrosis: Autosomal recessive. Portal hypertension is common.
Childhood-type polycystic disease: Autosomal recessive. Chronic liver and renal disease.
Adult-type polycystic disease: Autosomal dominant. Mild liver and renal disease.
Solitary (nonparasitic) liver cyst: Rare in childhood.

- Childhood-type polycystic disease is usually fatal in infancy or early childhood.
- Adult-type polycystic disease is usually asymptomatic.

B) SPLENOMEGALY

Isolated splenomegaly (without hepatic enlargement) is a common clinical finding, which can be caused by the following:

1. Infections: Acute or chronic infections are a common cause of splenomegaly. Prolonged fever is a common associated finding. Infectious mononucleosis, typhoid fever, brucellosis, malaria and visceral leishmaniasis (Kala azar) are the most common. Kala azar can lead to huge splenomegaly with or without hepatomegaly and lymphadenopathy. It can be diagnosed by splenic aspiration, bone marrow aspiration or lymph node biopsy.

2. Portal hypertension: Splenomegaly can be the sole manifestation of portal or splenic vein thrombosis (prehepatic portal hypertension). Other clinical findings as hematemesis (esophageal varices) or dilated abdominal wall veins may be also present. In advanced cases, hypersplenism with variable degrees of pancytopenia usually occur. History of neonatal umbilical sepsis or umbilical catheterization is important. Diagnosis is confirmed by Doppler abdominal ultrasonography.

3. Chronic hemolytic anemia: The clinical triad of pallor, icteric tinge and splenomegaly is characteristic of chronic hemolytic anemia. Positive family history and history of repeated transfusions are commonly present (see chronic hemolytic anemias).

4. Metabolic diseases: Several metabolic diseases especially lipidoses are associated with splenomegaly but the liver is usually enlarged to a lesser extent (see hepatosplenomegaly).

5. Tumors: Lymphoma and chronic myeloid leukemia should be excluded in a child with significant or huge splenomegaly. In lymphoma, lymphadenopathy is a common associated finding. In chronic myeloid leukemia, marked leukocytosis is characteristic (see common malignancies).

6. Splenic cysts: Splenic cysts can produce a splenomegaly, which may suggest a malignant neoplasm. Splenic cysts are two types: epidermoid cysts (lined with stratified epithelium) and pseudocysts (post-traumatic or post-infarction). Abdominal ultrasonography is essential for diagnosis.

C) HEPATOSPLENOMEGALY

There is no single satisfactory clinical classification of the causes of Hepatosplenomegaly. In fact, 3 factors should be considered:

1 The age of the patient.
2.The predominant enlarged organ (which is bigger?).
3. The associated clinical manifestations.

With this concept, causes of hepatosplenomegaly can be classified into 3 groups. It is important to remember that at any age group, chronic infections are an important cause that should be also considered.

(a) In neonatal period and early infancy

• In this age group, liver is usually bigger than the spleen because primary liver diseases are the main causes. Liver biopsy is necessary for diagnosis.

• The main associated clinical finding is ***jaundice***. In advanced cases, manifestations of chronic liver cell failure (ascites, edema, bleeding) and portal hypertension (splenomegaly, ascites, esophageal varices) occur.

• During this age group, the main causes are:

1. Neonatal hepatitis: Congenital infections, septicemia and idiopathic or giant cell hepatitis are the main causes.

2. Biliary atresia: Progressive jaundice, hepatomegaly and pale clay-colored stool are suggestive. In advanced cases, biliary cirrhosis occurs.

3. Metabolic liver disease: Galactosemia, tyrosinemia, alpha one antitrypsin deficiency are the main causes.

(b) In late infancy and early childhood

• In this age group, spleen is usually bigger than the liver because the diseases causing the enlargement are not primary liver diseases.

• The main associated clinical finding is *anemia*.

• During this age group, the main causes are:

1. Metabolic diseases: Gaucher disease and Niemann Pick disease are the most common metabolic diseases causing hepatosplenomegaly. Other causes as mucopolysaccharidosis, mucolipidosis, gangliosidosis, fucosidosis and mannosidosis are much less common and in all these conditions, mental retardation and coarse Hurler-like features are also present. Bone marrow examination and splenic aspiration are useful for diagnosis but enzymatic study of the cultured fibroblasts is the most reliable method for diagnosis and differentiation (see also metabolic diseases).

a) Gaucher disease is an autosomal recessive disease caused by glucocerebrosidase deficiency. The disease has 2 forms; the acute infantile form and the chronic adult form. *Acute infantile form* is characterized by splenomegaly and progressive neurological

disease (convulsions and motor weakness). *Chronic adult form* is by far more common and it usually presents in infancy with huge hepatosplenomegaly (spleen is always bigger). Diagnosis is confirmed by splenic biopsy or bone marrow examination, which reveals the characteristic Gaucher cells (large multinucleated cells with fibrillar nonvaculated cytoplasm).

b) Niemann Pick disease is an autosomal recessive disease caused by sphingomyelinase deficiency. The disease has 4 types (see metabolic diseases). In all types, hepatosplenomegaly is present and the liver may be larger than the spleen. Vaculated lymphocytes in peripheral blood, if present, are characteristic of Niemann Pick disease. Bone marrow reveals the foam cells (not peculiar to Niemann Pick but also present in other lipidoses).

Causes of metabolic hepatosplenomegaly

Without mental retardation

Gaucher disease: Characteristic Gaucher cells in bone marrow.
Niemann Pick disease: Foam cells in bone marrow.
Glycogenoses type IV: Ascites, cirrhosis and liver failure.
Osteopetrosis: Skeletal survey is diagnostic (marble bone disease).

With mental retardation

Mucopolysaccharidoses. Mucolipidoses. Gangliosidoses. Glycoproteinosis.	In these conditions, ***coarse hurler-like features*** are usually present (see metabolic diseases).

3. Acute leukemia: The clinical triad of anemia, purpura and hepatosplenomegaly in a child should always raise the possibility of acute leukemia especially when the duration of illness is only few weeks or months. Prolonged fever, arthritis and bone pains are also common. Diagnosis depends on demonstration of blast cells in peripheral blood and bone marrow.

Value of bone marrow examination in hepatosplenomegaly

Metabolic diseases: Demonstration of Gaucher cells or foam cells.
Chronic hemolytic anemia: Hyperactive bone marrow.
Acute leukemia: Demonstration of leukemic blast cells.

(c) In late childhood

- During this age group, liver is usually bigger than the spleen because primary liver diseases are the main causes.
- The main associated manifestations are those of chronic hepatic failure (jaundice, ascites, edema, bleeding) and portal hypertension (esophageal varices, ascites).
- The main causes during this age group are those of **chronic hepatitis** (see above).

9. Jaundice

Acute jaundice	Chronic jaundice
Acute liver disease	**Chronic liver disease**
Acute hepatitis	Chronic hepatitis
Liver abscess	Chronic cholestasis
Acute CHF	Chronic congestion
Reye syndrome	Metabolic liver disease
Acute hemolytic anemia	**Chronic hemolytic anemia**
G6PD deficiency	Structural defect
Crises of chronic hemolysis	Enzymatic defect
Autoimmune hemolytic anemia	Hemoglobinopathies
Hemolytic uremic syndrome	Chronic autoimmune hemolytic anemia
Infections (septicemia, malaria)	**Chronic nonhemolytic jaundice**
Metabolic (Wilson, porphyria)	Crigler-Najjar syndrome
	Gilbert disease

Jaundice is a common clinical presentation, which usually becomes evident when serum bilirubin exceeds 3 mg/dl. It can be acute or chronic. With determination of serum bilirubin level and its fractions, it can be classified as unconjugated and conjugated hyperbilirubinemia.

A) ACUTE JAUNDICE

1. Acute liver disease: Jaundice is usually associated with tender hepatomegaly, dark urine (bilirubinuria) and *conjugated hyperbilirubinemia*. Other clinical manifestations depend on the causative disease (for clinical and laboratory differentiation, see acute liver disease).

2. Acute hemolytic anemia: Jaundice is associated with intense pallor (acute hemolysis), pink to red urine (hemoglobinuria) and *unconjugated hyperbilirubinemia*. In severe cases, manifestations of acute hypoxia as tachypnea and altered consciousness (hypoxic anemic encephalopathy) are also present (see acute hemolytic anemia).

Conditions in which acute hepatitis and acute hemotytic anemia may coexist

Severe septicemia: Leukocytosis, high ESR and CRP, ± positive blood culture.
Malaria: Blood film for malaria.
Wilson disease: Low serum ceruloplasmin, high serum copper, increased urinary excretion of copper and increased copper content in liver biopsy.

B) CHRONIC JAUNDICE

1. Chronic liver disease: Chronic jaundice is usually associated with hepatomegaly and *conjugated hyperbilirubinemia*. Splenomegaly may be also present but the liver is usually bigger. Manifestations of chronic hepatic failure (ascites, edema, bleeding) and portal hypertension (esophageal varices, ascites) may be also present. Other clinical manifestations suggesting a specific disease may be present as arthritis (chronic hepatitis), pruritis and clay-colored stool (chronic cholestasis), chronic chest disease (cystic fibrosis), chronic heart disease (posthepatic portal hypertension) or chronic neurological disease (Wilson disease). Laboratory investigations to assess the hepatic function, structural integrity and to identify the causative disease are needed (see chronic liver disease).

2. Chronic hemolytic anemias: Chronic jaundice is associated with chronic anemia and splenomegaly. Hepatomegaly may be also present but the spleen is always bigger. Positive family history or history of repeated transfusions is commonly obtained. Laboratory diagnosis depends on the presence of mild *unconjugated hyperbilirubinemia*, chronic anemia, reticulocytosis, high serum iron, low iron binding capacity and hyperactive bone marrow. Diagnosis of the cause of hemolysis requires morphological study of the red cells, enzymatic study, Coombs test and hemoglobin electrophoresis (see chronic hemolytic anemias).

3. Chronic nonhemolytic jaundice: Chronic jaundice without hepatomegaly or splenomegaly should always raise the possibility. Laboratory diagnosis depends on the presence of *unconjugated hyperbilirubinemia* without evidence of chronic hemolysis. The main causes are:

a) Crigler-Najjar syndrome: It has 2 types. *Type I* is an autosomal recessive disease caused by absent hepatic glucuronyl transferase activity and is characterized by severe hyperbilirubinemia (above 20 mg/dl) starting in early neonatal period. *Type II* is an autosomal dominant disease caused by deficient glucuronyl transferase activity and is characterized by mild to moderate hyperbilirubinemia (5-20 mg/dl) starting in neonatal period or later in infancy or childhood (see also neonatal jaundice).

b) Gilbert disease: It is an autosomal dominant disease caused by an uptake defect of liver cell membrane, which impairs bilirubin uptake. It is a mild benign disease characterized by mild or even unnoticed jaundice. Serum bilirubin level is usually below 5 mg/dl.

9

Urinary System

- **Urinary Diseases.**

1. **Dark Urine.**
2. **Edema.**
3. **Dysuria.**
4. **Polyuria.**
5. **Enuresis.**
6. **Hypertension.**
7. **Renal Failure.**

Urinary Diseases

Nephrotic diseases	Urologic diseases
Glomerular diseases	**Urinary tract infections**
Glomerulonephritis	Upper infections (pyelonephritis)
Nephrotic syndrome	Lower infections (cystitis, urethritis)
Tubular diseases	**Obstructive uropathy**
Renal tubular acidosis	Upper (ureteric) obstruction
Nephrogenic diabetes insipidus	Lower (bladder or urethral) obstruction
Other renal diseases	**Urinary calculi or stones**
Renal anomalies (dysplasia, polycystic kidney)	Upper stones
Renal vascular disease (thrombosis)	Lower stones
Renal tumors (Wilms tumor, others)	**Funtional abnormality**
	Vesicoureteral reflux

Diseases of the urinary system may affect the kidneys, collecting system or both. Glomerulonephritis, nephrotic syndrome, urinary tract infection and renal failure are by far the most common.

Urinary diseases can present with urinary and/or extraurinary presentations.

- ***Urinary presentations*** are directly related to urine and include hematuria (dark urine), proteinuria, dysuria, polyuria, oliguria, urinary retention and enuresis.
- ***Extraurinary presentations*** include edema, hypertension, abdominal pain, abdominal mass, ascites, unexplained prolonged fever, chronic vomiting, growth failure, chronic anemia and rickets.

In all these presentations, urinary diseases should be considered.

Clinical presentations of urinary diseases

Glomerulonephritis: Hematuria, edema, hypertension.
Nephrotic syndrome: Massive proteinuria, generalized edema, ± hypertension.
Urinary tract infection: Fever, vomiting, abdominal pain, dysuria, pyuria.
Acute renal failure: Oliguria or anuria, metabolic acidosis, ± coma.
Chronic renal failure: Chronic vomiting, growth failure, hypertension, anemia, rickets.
Renal tubular acidosis: Chronic vomiting, growth failure, chronic acidosis.
Renal anomalies: Abdominal mass.
Renal vascular disease: Abdominal mass, hematuria.
Renal tumours: Abdominal mass, ± hematuria.
Obstructive uropathy: Abdominal mass, ± retention of urine.
Urinary calculi: Dysuria, hematuria, abdominal pain.

1. Dark Urine

Hematuria	Other causes
Glomerular diseases Poststreptococcal glomerulonephritis Rapidly progressive glomerulonephritis Membranoproliferative glomerulonephritis Nephritis with other diseases Henoch-Schonlein Vasculitis Systemic lupus erythematosus Chronic infections Gross recurrent hematuria IgA nephropathy Alport syndrome Benign recurrent hematuria Hemolytic uremic syndrome **Other renal diseases** Renal vein thrombosis Renal tumours **Urological diseases** Urinary tract infection Urinary stones or calculi **Physical causes** Traumatic hematuria Exercise hematuria **Hematological bleeding disorders**	**Bilirubinuria** With active liver disease (urine is dark yellow to orange) **Hemoglobinuria** with acute hemolytic anemia (urine is pink to red) **Urate crystalluria** With urate stones or crystals (urine is pink) **Foods and drugs** **Foods:** Beet roots Red food colouring **Drugs:** Rifampicin Metronidazole Vitamin B complex Several other drugs **Rare diseases** Porphyria (red urine) Myoglobinuria (pink to red) Blue diaper syndrome (Blue urine) Alkaptonuria (black urine)

The color of normal urine may range from pale yellow or almost colorless to amber yellow depending on the amount of fluid intake and the type of eaten foods.

Changes in the urine color can be simply caused by ingestion of certain foods, drinks or drugs or may reflect several diseases of different origins. Hematuria, bilirubinuria and hemoglobinuria are the most common. The color of the urine can give a diagnostic clue to the underlying cause or disease.

Diagnostic significance of changes in urine color

Dark yellow: Concentrated urine, vitamin B complex, bilirubinuria.
Pink urine: Urate crystals, hemoglobinuria, foods and drugs.
Red urine: Hematuria, hemoglobinuria, myoglobinuria. porphyria, foods and drugs.
Brown urine: Hematuria of renal origin (tea-colored or cola-colored).
Black urine: Hematuria, alkaptonuria.
Blue urine: Blue diaper syndrome.

Diagnosis of hematuria

Hematuria (blood in urine) is a common clinical presentation in pediatric practice. The condition should be clinically considered when the urine is pink to red or brown (tea-colored or cola-colored). In absence of jaundice, acute intense pallor and recent drug intake, the dark urine is mostly due to the presence of blood.

With clinical evaluation and simple urine examination, hematuria can be classified according to the amount of blood, origin of blood and presence or absence of symptoms.

Types of hematuria

According to the amount of blood

- Gross hematuria: Visible by the naked eye (pink to red or brown urine).
- Microscopic hematuria: Detected only by microscopic examination.

According to the origin of blood

- Renal (or nephrologic) hematuria: Urine is brown (tea-colored or cola-colored)
  RBCs casts and proteinuria are common.
  Edema and hypertension are common.
- Extrarenal (or urologic) hematuria: Urine is pink to red.
  Blood clots, pyuria or crystalluria is common.
  Dysuria and abdominal pain are common.

According to the presence or absence of symptoms

- Symptomatic hematuria: Associated with other symptoms.
  May be painful (with dysuria) or painless.
- Asymptomatic hematuria: No other symptoms.

- Initial diagnosis of hematuria should include the 3 aspects (amount, origin, symptoms).
- Examples of diagnosis are:
  * Gross renal symptomatic hematuria
  * Microscopic renal asymptomatic hematuria
  * Gross extrarenal symptomatic hematuria

Diagnosis of the cause of hematuria can be made by clinical evaluation and laboratory investigations.

Possible investigations in case of hematuria

Complete urine analysis and urine culture: In ALL cases.
Evaluation of renal function (blood urea and creatinine): In ALL cases.
Abdominal ultrasonography: In ALL cases.
Complete blood count (CBC) and serum complement 3 (C3) level: In ALL cases.
Other investigations:

Throat culture and ASO titre: With suspected poststreptococcal glomerulonephritis.
Coagulation studies and platelet count: With suspected bleeding disorder.
Voiding cystourethrography or cystoscopy: With recurrent or persistent urologic hematuria.
Renal biopsy: With recurrent or persistent hematuria.

(a) Bleeding disorders

As in every case of external bleeding from any orifice, bleeding disorders should be excluded. Clinically, history of bleeding from any other orifice or cutaneous manifestations as purpura, bruising or hematomas are suggestive. Laboratory exclusion is by coagulation studies and platelet count. It is important to note that thrombocytopenia may accompany some glomerular diseases as in hemolytic uremic syndrome and nephritis of systemic lupus.

(b) Glomerular diseases

1. Acute poststreptococcal glomerulonephritis: It is the commonest cause of hematuria in children above the age of 3 years. It is an autoimmune disease following group A beta hemolytic streptococcal infection of the throat or the skin. History of preceding pharyngitis or skin pyoderma 1-3 weeks before the onset of illness is usually obtained.

- ***Clinically***, it has 3 presentations:

a) Acute nephritic syndrome: Most patients present acutely with dark urine (hematuria), oliguria, periorbital edema and hypertension. Mild fever, anorexia, vomiting and headache are usually present. Hematuria is gross (urine is smoky brown, tea or cola-colored) initially but the urine usually becomes clear at the end of the first week. Edema is usually mild (puffy eyes and edema of extremities) but it may be generalized in 3 conditions: (1) renal failure with unrestricted fluid intake, (2) heart failure and (3) associated nephrosis. Hypertension is present in 70% of cases and it may be as high as 200/120. It usually returns to normal slowly at the end of the first week. Acute renal failure is usually mild and transient in most cases. However, severe renal failure with marked oliguria or anuria, acidotic breathing and generalized edema may occur.

b) Hypertensive heart failure: Some patients present with respiratory distress and manifestations of acute heart failure (tachycardia, tachypnea and tender liver). Heart failure is actually multifactorial and it is caused by hypertension (afterload failure), hypervolemia due to severe oliguria with unrestricted fluid intake (preload failure) and myocardial ischemia (contractility failure). Blood pressure should be measured in every case of heart failure.

c) Hypertensive encephalopathy: Some patients present with altered consciousness and/or convulsions and are wrongly diagnosed as CNS infection. Blood pressure should be measured in any child presenting with altered consciousness or convulsions.

- ***Laboratory diagnosis*** depends on the presence of high level of serum antistreptococcal antibodies (high ASO titer) and low serum complement 3 level (normal level is 70 - 200 mg/dl). It is important to remember that complement 3 level is also low in membranoproliferative glomerulonepharitis and nephritis of systemic lupus but both conditions usually do not occur before the age of 10 years.

- ***Prognosis*** of poststreptococcal glomerulonephritis is excellent. Complete recovery within few weeks is the rule. Microscopic hematuria may remain for several months.

2. Rapidly progressive (crescentic) glomerulonephritis: Rapid progresssion of glomerulonephritis to renal failure in few weeks or months should suggest the diagnosis. The condition may follow other types of glomerulonephritis including poststreptococcal glomerulonephritis. It has a characteristic renal biopsy (crescents are found on the inside of Bowman capsule). Prognosis is generally poor but spontaneous recovery may occur especially in cases following poststreptococcal glomerulonephritis.

3. Membranoproliferative (mesangiocapillary) glomerulonephritis: It is the most common cause of chronic glomerulonephritis in children above the age of 10 years. Prognosis is generally poor as most cases progress to chronic renal failure. It has 3 pathological types. Type I is the most common and it is associated with low serum complement 3 level. The condition should be suspected in any child above 10 years with persistent nephritis or nephrotic syndrome. Diagnosis is made by renal biopsy.

4. Nephritis with other diseases: Nephritis may accompany other diseases but in these conditions it is usually not the main presentation. Henoch-Schonlein vasculitis, systemic lupus erythematosus and chronic infections especially infective endocarditis are the most common examples. Goodpasture disease is a very rare disease characterized by pulmonary hemorrhage and glomerulonephritis.

5. Recurrent gross hematuria (RGH): Recurrent gross hematuria can be painless or painful. *Painless hematuria* is mostly caused by glomerular diseases as IgA nephropathy, hereditary nephritis and familial hematuria. Differentiation between these conditions depends on renal biopsy, which is indicated with the second episode. *Painful hemauria (dysuria)* is mostly caused by urological diseases as recurrent urinary tract infection (hemorrhagic cystitis or bilharziasis) and urinary calculi.

a) IgA nephropathy (Burger disease): It is the most common chronic glomerular disease in children. The attacks of gross hematuria are usually precipitated by minor respiratory infections and each episode usually resolves over 1-2 weeks but microscopic hematuria usually persists between the attacks. Renal function and prognosis are good in most cases but in 20% of cases, progressive renal disease occurs several years after onset with hypertension and impaired renal function (prolonged follow up is important). Immunofluorescence studies can demonstrate the glomerular IgA mesangial deposits.

b) Hereditary nephritis (Alport syndrome): t is an x-linked dominant or autosomal dominant disease, which is clinically similar to Burger disease. Hearing loss and eye abnormalities may occur in some patients (audiogram and ophthalmologic examination are very important). Prognosis is bad as most patients pass to chronic renal failure and end-stage renal disease (ESRD) in the second or third decade. Prolonged follow up and renal biopsy are needed for differentiation from Burger disease. Electron microscopy reveals thickening, thinning, splitting and layering of glomerular basement membranes.

***c) Benign familial hematuria*:** This benign condition is also known as *thin glomerular basement membrane disease* (TGBMD) because thinning of the glomerular basement membrane is the only finding on electron microscopy. It has an excellent prognosis with no affection of renal function. It is characterized by normal renal biopsy on light and immunofluorescence microscopy. Prolonged follow up is important to exclude Alport syndrome because histological changes in initial biopsy may be similar.

6. Hemolytic uremic syndrome: It is the most common cause of acute renal failure in children below the age of 4 years. History of preceding gastroenteritis or upper respiratory infection 5-10 days before the onset of illness is usually obtained. Clinically, the onset is abrupt with manifestations of acute hemolytic anemia (intense pallor), acute renal failure (oliguria, acidotic breathing, altered consciousness) and thrombocytopenia (purpura). Laboratory diagnosis reveals evidence of acute hemolysis (severe anemia, reticulocytosis, fragmented red cells), acute renal failure (elevated blood urea and creatinine, metabolic acidosis, hyperkalemia) and thrombocytopenia (20,000 - 100,000 /mm^3 10^9 L). Prognosis depends on the proper management of acute renal failure. The illness should be differentiated from other causes of acute renal failure especially bilateral renal vein thrombosis, which is also characterized by the triad of acute hemolytic anemia, acute renal failure and thrombocytopenia. With bilateral renal vein thrombosis, hematuria is usually gross and the kidneys are markedly enlarged.

(c) Other renal diseases

1. Renal vein thrombosis: It usually complicates other critical illness as in neonates with severe hypoxia and sepsis or infants with severe gastroenteritis and dehydration. It may also occur with cyanotic heart disease or with the use of angiographic contrast agents. Gross hematuria with unilateral or bilateral flank masses is the main presentation. Unilateral involvement is commoner and it does not lead to acute renal failure. Bilateral renal vein thrombosis results in acute renal failure, acute hemolytic anemia and thrombocytopenia and should be differentiated from hemolytic uremic syndrome. Abdominal ultrasonography and Doppler flow studies are necessary for diagnosis.

2. Renal tumours: Hematuria may occur in Wilms tumor but it is usually not the main presentation. Abdominal mass in the right or left upper quadrant is the main presentation (see abdominal masses and common malignancies).

(d) Urological diseases

1. Urinary tract infection: Gross or microscopic hematuria associated with urgency or dysuria should suggest the possibility of hemorrhagic cystitis or urethritis. Diagnosis is confirmed by the presence of pyuria and bacteriuria. Urinary bilharziasis should be considered in older children of rural endemic areas.

2. Urinary calculi: Recurrent attacks of gross or microscopic hematuria with abdominal pain or dysuria should suggest the possibility of urinary stones.

Diagnosis of urinary calculi should include the following 4 steps:

1. Detection of the calculi.
2. Identification of the type.
3. Identification of the predisposing factors.
4. Evaluation of renal function.

Diagnostic approach of urinary calculi

Detection of the calculi

Plain x-ray of the all abdomen: To detect radio-opaque stones as calcium oxalate.
Abdominal ultrasonography: To detect radio-opaque or radiolucent stones.
Intravenous pyelography: To demonstrate filling defects.

Identification of the type (oxalate, urate, cystine)

Urine analysis: Analysis of crystalluria.
Endoscopic or surgical extraction of the stones.

Identification of the predisposing factors

Structural abnormalities (as obstructive uropathy): Abdominal ultrasonography.
Functional abnormalities (as vesicoureteral reflux): Voiding cystourethrography.
Metabolic disorders (as hypercalcemia, hyperuricemia): Serum calcium, uric acid.
Urinary tract infection: Repeated urine culture.

Evaluation of the renal function

Blood urea and serum creatinine.

(e) Physical causes of hematuria

1. Traumatic hematuria: Blunt or penetrating trauma to the kidney may result in gross or microscopic hematuria. When minor blunt trauma results in gross hematuria, congenital anomalies of the urinary system especially cystic kidneys should be excluded. Urethral trauma following crush injury, instrumentation or by foreign body should be also considered.

2. Exercise hematuria: Vigorous exercise may result in microscopic or gross hematuria, which usually resolves within 2 days. The condition is benign and the source of bleeding is mostly from the lower urinary tract.

2. Edema

Renal edema	Nonrenal edema
Nephrotic syndrome	**With hypoprteinemia**
Idiopathic NS	Nutritional edema
Minimal change disease (commonest).	Hepatic edema
Focal segmental sclerosis.	Protein losing enteropathy
Mesangial proliferation.	
Congenital nephrosis	**Without hypoprteinemia**
Secondary NS	Cardiac edema
Memberonoproliferative glomerulonephritis	Allergic edema
Infections (hepatitis B, malaria)	Iatrogenic edema
Rheumatoid arthritis and SLE	Lymphatic edema
Malignancies (Hodgkin disease)	Hereditary angioedema
Other renal causes	
Glomerulonephritis, Renal failure	

Edema is a common clinical presentation in pediatric practice, which can be caused by renal or nonrenal conditions. Clinical diagnosis of the cause is not difficult in most cases and it depends on:

1. Distribution of edema: Is it localized or generalized?
2. Onset and duration: Is it acute or chronic?
3. Associated clinical manifestations: Renal, nutritional, hepatic, intestinal, cardiac or allergic manifestations.

A) RENAL EDEMA

1. Nephrotic syndrome: It is the most common cause of generalized edema in children above the age of 2 years. Edema is the only striking clinical feature and other urinary manifestations as hematuria and hypertension are usually absent. Diagnosis is confirmed by the presence of massive proteinuria, hypoproteinemia and hyperlipidemia (see below).

2. Other renal causes: ***Poststreptococcal glomerulonephritis*** is a common cause of localized transient periorbital and ankle edema. However, generalized edema may occur when complications as acute renal failure or acute heart failure occur. With glomerulonephritis, hematuria and hypertension are the main presentations. ***Acute renal failure*** may be also accompanied with generalized edema especially when severe oliguria or anuria is accompanied with unrestricted fluid intake resulting in fluid retention. With acute renal failure, clinical and laboratory evidence of renal failure are well evident (see acute renal failure).

B) NONRENAL EDEMA

1. Nutritional edema: Kwashiorkor is the most common cause of edema between 6 months and 2 years in underdeveloped countries. History of deficient protein intake and other characteristic manifestations are usually evident (see protein calorie malnutrition).

2. Hepatic edema: Acute and chronic hepatic failure can be accompanied with generalized edema due to decreased protein synthesis and hypoproteinemia. Other clinical manifestations suggesting hepatic origin as hepatomegaly and jaundice are usually evident (see hepatomegaly and jaundice).

3. Protein losing enteropathy: Protein loss through the gut may accompany cases of malabsorption and can be transient (following severe gastroenteritis) or persistent (with chronic diarrhea). However, the condition should be also considered in every case of unexplained edema (even without diarrhea) especially when it is associated with hypoproteinemia.

4. Cardiac edema: Acute and chronic congestive heart failure can be accompanied by localized or generalized edema. The clinical manifestations of heart failure are the dominating features.

5. Allergic edema: Severe allergic reactions as with giant urticaria or serum sickness may be associated with generalized edema. The acute onset of the condition and the associated urticarial rash and itching make no diagnostic difficulty.

6. Iatrogenic edema: Over-infusion in patients receiving I.V. fluids leads to overhydration with puffiness of eyelids, hardening of the skin and generalized edema. However, the condition may also occur with properly calculated amount if the patient is having acute renal failure or inappropriate secretion of antidiuretic hormone. These 2 complications should be considered in every sick patient receiving I.V. fluids.

7. Lymphatic edema: Edema due to lymphatic obstruction is rare. Milroy disease in newborns and intestinal lymphangiectasia in infants and children are the main examples. With intestinal lymphangiectasia, edema may be asymmetric and ascites or chronic diarrhea may be also present. Lymphatic edema should be also suspected in every case of unexplained edema without hypoproteinemia.

Causes of unexplained edema

Protein losing enteropathy: Hypoproteinemia is usually present.

Lymphatic edema: Hypoproteinemia is usually absent.

Hereditary angioedema: Autosomal dominant disease due to deficiency of complement 1 inhibitor (C1 inhibitor deficiency). Repeated attacks of edema following vigorous exercise or with emotional stress is the main presentation. Each attack usually lasts for 2-3 days.

Diagnosis of nephrotic syndrome

Nephrotic syndrome is a clinico-laboratory syndrome of 4 components. It is the commonest cause of generalized edema in children. The basic defect is increased protein loss in urine (proteinuria) due to increased permeability of glomerular capillary wall. This will result in hypoproteinemia and generalized edema.

Diagnostic criteria of nephrotic syndrome

Generalized edema: Swollen eye lids, puffy face, edematous limbs.
Scrotal edema (in males) and abdominal wall edema.
Ascites (abdominal enlargement), pleural effusion (dyspnea).

Massive proteinuria: Above 2 gm/24 hours. Levels above 5 -10 gm/24 hours are not unusual (normal urinary proteins is below 150 mg/24 hours).

Hypoproteinemia: Serum albumin below 2.5 gm/dl (normal level is above 4 gm/dl).

Hypercholesterolemia : Serum cholesterol level above 300 mg/dl (normal level is 120-220 mg/dl).

Nephrotic syndrome should not be confused with other causes of proteinuria.

Causes of proteinuria (other than nephrotic syndrome)

Transient proteinuria
Fever (above 38.5C°), exercise, stress, cold exposure, dehydration, congestive heart failure.

Postural (orthostatic) proteinuria
Persistent asymptomatic proteinuria, which is present in upright position only.

Fixed proteinuria
Glomerular: All causes of glomerulonephritis. Hematuria is the main presentation.
Tubular: Inherited (with renal tubular acidosis) or acquired (drugs).

- In ALL these conditions, edema is absent and proteinuria is below 1 gm/24 hours.

Diagnosis of nephrotic syndrome should include the associated manifestations (or complications) and the cause of the disease.

(a) Associated manifestations or complications

Clinical evaluation of nephrotic syndrome should include measurement of blood pressure, temperature, careful skin examination, abdominal examination and inspection of the urine. Laboratory evaluation should also include evaluation of the renal function. The most important associated manifestations or complications are:

1. Hypertension and hematuria: Significant or persistent hypertension or hematuria are absent in minimal change nephrotic syndrome but are common with other causes.

2. Infections: It is important to remember that nephrotic syndrome is an afebrile disease, so the presence of fever usually indicates infection. Peritonitis (abdominal tenderness), cellulitis (skin erythema) and septicemia (high fever) are the most common and should be routinely excluded.

3. Deterioration of renal function: Renal function is always normal and prognosis is excellent in minimal change disease. In other conditions, gradual deterioration of renal function is common. ***Renal biopsy*** is indicated in the following situations (1) age of onset below 1 year or above 10 years, (2) Persistent hypertension or hematuria, (3) failure of response to steroid therapy (after one month of daily therapy), (4) frequent recurrences and (5) deterioration of renal function.

(b) Cause of nephrotic syndrome

Nephrotic syndrome can be idiopathic, secondary or congenital. Idiopathic nephritic syndrome is by far the most common (90% of all cases) and it has 3 pathological types: (1) minimal change disease (85% of cases), (2) focal segmental sclerosis (10% of cases) and (3) mesangial proliferation (5% of cases).

1. Minimal change disease: It is the most common and it is characterized by:

1. Age of onset is between 2 - 6 years. However, it may occur earlier or later.
2. There is no significant or persistent hypertension or hematuria.
3. Proteinuria is selective (mainly albuminuria).
4. It has an excellent therapeutic response to steroid therapy.
5. It is a disease of remissions and exacerbations. Several relapses may occur but without deterioration of renal function.
6. Renal biopsy: Under light microscope, the glomeruli are free. Electron microscopy reveals fusion of the epithelial foot processes of the glomerular capillary wall.

2. Focal segmental sclerosis and mesangial proliferation: They cannot be clinically distinguished from minimal change disease but they should be suspected in cases not responding to steroid therapy or in cases with frequent relapses. With electron microscopy, the characteristic pathological changes are seen.

3. Membranous and membranoproliferative glomerulonephritis: These 2 conditions are characterized by the flowing:

1. Age of onset above 10 years (in the second decade).
2. Persistent hypertension or hematuria is common.
3. Proteinuria is usually nonselective (loss of all proteins).
4. Poor response to steroid therapy. Cytotoxic drugs are usually needed.
5. Most cases progress to chronic renal failure.
6. Renal biopsy demonstrates the pathological type.

4. Other causes: ***Congenital nephrosis*** has an onset in early infancy. ***Secondary nephrosis*** may follow infections (hepatitis B, malaria), rheumatic diseases (rheumatoid arthritis) or Hodgkin disease.

3. Dysuria

Urinary tract infection	Other causes
Upper infections	**Perineal and urethral irritation**
Pyelonephritis	Severe napkin dermatitis
Pyonephrosis	Inflammation of external genitalia
Lower infections	Meatal irritation or ulceration
Cystitis	Oxyuris
Urethritis	**Urinary stones or calculi**

Dysuria (painful micturition) is a common complaint in pediatric practice. In infants and young children, history of screaming during urination is the main presentation. The main causes of dysuria are the following:

1. Perineal and urethral irritation: Although urinary tract infection is usually incriminated as the first possibility, perineal and urethral irritation are probably commoner especially in infants and should be routinely excluded. ***Severe napkin dermatitis*** in infants is commonly associated with screaming during urination. ***Inflammation of external genitalia*** especially in females with vulvitis or vulvovaginitis is also an important cause. In male infants, ***meatal irritation or ulceration*** due to prolonged contact with wet diapers is an important cause. Occasionally, meatal irritation is observed in males who are not circumcised. ***Oxyuris*** is also an important cause. Although the main complaint with oxyuris is nocturnal anal pruritis and sleeplessness, dysuria may be also present especially in young females due to migration of the worms at night to enter the urethra.

2. Urinary tract infection: Infection of the urinary tract is much commoner in females (except in newborns). Colonic bacteria especially E. coli is by far the most common causative organism (80 - 90% of cases), followed by klebsiella and proteus.

- Urinary tract infections are commonly asymptomatic and when symptoms appear, they may be nonspecific and not directly related to the urinary system, so a high index of suspicion is important. Clinical presentations vary according to the age and to site of infection. However, it is frequently difficult to assess whether the infection is only limited to the lower urinary tract or also involving the kidneys. With clinical suspicion, laboratory investigations (urine analysis, urine culture) are essential for diagnosis.

- Laboratory diagnosis of urinary tract infection depends on the presence of bacteriuria (bacteria in normally sterile urine) with or without pyuria (leukocytes or pus cells in urine more than 4 -6/HPF). Collection of a *clean midstream sample of urine* is extremely important because contamination is a common cause of error. ***Urine culture*** is the only reliable investigation. Presence of more than one organism should indicate contamination. Other investigations may be also indicated.

Clinical presentations of urinary tract infection

Newborns: Fever, jaundice.

Infants: Fever, vomiting, abdominal pain, irritability.
Screaming during urination.

Children: Urinary symptoms (dysuria, urgency, dripping, foul smelling urine).
Secondary nocturnal enuresis.
Hematuria (with hemorrhagic cystitis or urethritis).
High fever, rigors and flank pain (with pyelonephritis).
Chronic hypertension (with chronic pyelonephritis and reflux nephropathy).
Prolonged unexplained fever.

Investigations (at least urine analysis and urine culture) are essential for diagnosis.

Diagnostic investigations of urinary tract infection

Urine analysis (For detection of pyuria)

Numerous cells are usually present in acute infection. However, it is unreliable because false positive and false negative results are common (see below).

Urine culture (For detection of bacteriuria)

It is the only reliable test.
Presence of more than one organism in culture indicates contamination.

Other investigations

Abdominal ultrasound: With suspected pyelonephritis, pyonephrosis.
CBC and CRP: With suspected pyelonephritis.

Investigations of recurrent urinary tract infection

Abdominal x-ray: To exclude radio-opaque urinary calculi.
Abdominal ultrasound: To exclude obstructive uropathy and reflux nephropathy.
Intravenous pyelography (IVP): To exclude obstructive uropathy.
Voiding cystourethrography (VCUG): It is very important to exclude vesicoureteral reflux.
Evaluation of renal function: To exclude chronic renal failure.

- **False negative result** is urinary tract infection without pyuria as with closed infection, obstructive lesions, and With antibiotic therapy. **False positive result** is pyuria without infection as with febrile illnesses, dehydration and poststreptococcal glomerulonephritis.

- **Vesicoureteral reflux** is the retrograde flow of urine from the bladder to the ureter and renal pelvis. The reflux predisposes to renal infection (pyelonephritis) and the inflammatory reactions lead to renal injury and scarring (reflux nephropathy).
  - The reflux can be primary (due to incompetence of the valvular mechanism of vesicoureteral junction) or secondary (due to severe bacterial cystitis or bladder dysfunctions).
  - Extensive scarring leads to recurrent infections, hypertension and chronic renal failure (reflux nephropathy is the cause of end-stage renal disease in 20% of cases).
  - Diagnosis and grading of severity is made by Voiding cystourethrography (VCUG). There are 5 grades (grade I to grade V). Grade I is mild reflux while grade V is massive reflux.

4. Polyuria

Endocrinal	Metabolic	Psychogenic
Diabetes mellitus Diabetes insipidus	Hypercalcemia Renal tubular acidosis Chronic renal failure	Compulsive water drinking (mainly in adolescent females with psychological disorders)

The complaints of ***polyuria*** (increased urine output) and ***polydipsia*** (excessive drinking) usually coexist. In most cases, polyuria is the cause of polydipsia except in compulsive water drinking. *Secondary nocturnal enuresis* is a common associated finding and may be even the initial alarming complaint (see enuresis). History *of failure to thrive or recent history of weight loss* is important indirect presentation, which should also raise suspicion.

Laboratory evaluation in patients with polyuria

Urine analysis: Volume per 24 hours, osmolarity, presence of glucosuria.
Blood sugar level.
Serum electrolytes: Especially calcium, potassium, sodium and chloride.
Acid-base balance (blood gases) for detection of metabolic acidosis.
Evaluation of renal function for detection of chronic renal failure.
Response to water deprivation and vasopressin: With suspected diabetes insipidus.

1. Diabetes mellitus: It is the commonest cause of polyuria and polydipsia in children. The duration of symptoms is usually less than one month in most cases. Diagnosis depends on presence of glucosuria and hyperglycemia (see endocrinology).

2. Diabetes insipidus: Antidiuretic hormone deficiency can be inherited or acquired (encephalitis, craniopharyngioma). Severe polyuria, polydipsia, vomiting, constipation and growth failure are the main features. Diagnosis depends on 3 criteria:

1. Severe polyuria (urine volume/24 hours is more than 4 liters).
2. Impaired ability to concentrate urine: Low specific gravity (below 1005) and low urine osmolarity (below 200 mOsm/kg water). Even after water deprivation test for 6 hours, urine osmolarity characteristically remains low.
3. Therapeutic response to desmopressin: Rapid rise of urine osmolarity occurs. In patients with nephrogenic diabetes insipidus (antidiuretic hormone unresponsiveness), there is no response to desmopressin.

3. Hypercalcemia: It should be routinely excluded in every case of polyuria with impaired ability to concentrate urine (low specific gravity and osmolarity). Other clinical manifestations as anorexia, vomiting and constipation may be also present. Diagnosis depends on the presence of high serum calcium level (above 13 mg/dl). The main causes are vitamin D intoxication (history of vitamin D intake is very important).

idiopathic hypercalcemia (mental retardation, odd-looking face, aortic stenosis) and hyperparathyroidism (high serum calcium with low serum phosphorus). Other causes include vitamin A intoxication, prolonged immobilization, subcutaneous fat necrosis, malignant tumours and hypophosphatasia.

4. Renal tubular acidosis: It is the commonest cause of chronic hypokalemia. The condition usually presents with failure to thrive, chronic vomiting and repeated episodes of acute metabolic acidosis. Laboratory diagnosis depends on the presence of chronic hyperchloremic metabolic acidosis (metabolic acidosis with increased serum chloride level) without significant reduction in glomerular filtration rate (no significant increase in blood urea or serum creatinine). It has 4 types (distal type, proximal type, mixed type with features of proximal and distal types and hyperkalemic type). Normal renal function is an important differentiating point from chronic renal failure.

Types of renal tubular acidosis

	Distal type (Type I)	Proximal type (type II)	Hyperkalemic type (type IV)
Mechanism	Impaired urinary acidification → acid retention	Impaired bicarbonate reabsorption → bicarbonate loss	Impaired aldosterone production → hyperkalemia
Causes	Sporadic Inherited Interstitial nephritis	Sporadic Inherited Fanconi syndrome	Sporadic Inherited Obstructive uropathy
Urine pH	Above 5.8	Acidic (below 5.5)	Alkaline or acidic
Serum Potassium	Low	Low	High
Other features	Hypercalciuria and nephrocalcinosis	Rickets	High urinary sodium

• Causes of **Fanconi syndrome** are discussed with rickets.

• **Bartter syndrome** is a rare disease characterized by renal potassium loss due to decreased tubular reabsorption of chloride. Diagnosis depends on presence of hypokalemia, hypochloremia and metabolic alkalosis. Elevated plasma level of renin and aldosterone are also present.

5. Chronic renal failure (CRF): Evaluation of renal function is important in every case of polyuria to exclude CRF. Other clinical presentations include failure to thrive, chronic vomiting, chronic anemia, chronic hypertension and rickets (above the age of 4 years). Laboratory diagnosis depends on the presence of persistent elevation of blood urea and serum creatinine level. Several other biochemical abnormalities including chronic metabolic acidosis are also present (see renal failure).

6. Compulsive water drinking (Psychogenic polydipsia): It usually occurs in adolescent females with emotional disorders (as anxiety) or psychosis. There is normal renal function and normal ability to concentrate urine with water deprivation.

5. Enuresis

Primary enuresis	Secondary enuresis
Maturational delay Primary nocturnal enuresis	**Emotional stress**
Organic causes Mental retardation Anomalies (sacral, urological)	**Organic causes** Urinary tract infection Polyuria

Enuresis is the repeated involuntary voiding (urination) beyond the expected age of bladder control. As the normal bladder control is usually attained between the ages of 2-4 years, the term enuresis should be limited to children above the age of 4 years.

Types of enuresis

According to onset

Primary enuresis (80% of cases): It is a continuation of the involuntary control in earlier years (i.e. the child has never attained a bladder control).

Secondary enuresis (20% of cases): It is the involuntary voiding in a previously trained child (a period of at least 6 months of bladder control is essential before considering the enuresis as a secondary).

According to timing

Nocturnal enuresis (majority of cases): It is a night-time incontinence or "bed wetting. The prognosis for recovery is generally good.

Diurnal enuresis (minority of cases): It is a both day-time and night-time incontinence, i.e. "continuous wetting'. It is a severe form with a less favourable prognosis and it is commonly associated with encopresis (involuntary soiling or defecation).

Primary nocturnal enuresis is by far the most common type.

• ***Clinical evaluation*** of children with enuresis should include the following:

1. Type of enuresis (primary or secondary and nocturnal or diurnal).
2. Severity of enuresis (number of wet nights per week).
3. Associated clinical manifestations: In primary cases, mental retardation, sacral anomalies (spina bifida, meningocele) and urological anomalies should be routinely excluded. If possible, observation during micturition is useful for detection of urological abnormalities as deviated stream or dripping, which may accompany bladder neck or urethral anomalies. In secondary cases, urinary tract infection and polyuria should be excluded. History of emotional stresses should be considered in secondary enuresis.

• ***Simple urine analysis*** should be a routine step in every case to exclude organic causes especially polyuria and urinary tract infection.

A) PRIMARY ENURESIS

1. Primary nocturnal enuresis: It is by far the most common type of enuresis.

- It occurs in 20% of children at the age of 5 years and 10% at the age of 8 years (in adults, it is less than 1% which demonstrates the benign nature of the condition).
- It is 3 times *commoner in boys* than in girls and it is also commoner in the first-born child and in low socioeconomic classes.
- A *strong family history* is present (30% of fathers and 20% of mothers had a history of childhood enuresis. The same incidence is obtained with older brothers and sisters).
- The *severity* of enuresis is variable from one child to another but daily wetting is common in most cases. The condition may be exaggerated by parental punishment or humiliation. On the other hand, understanding, encouragement and simple rewards may be helpful. It is important to remember that enuresis is the sole clinical manifestation and clinical evaluation reveals no other abnormalities.
- The *prognosis* for ultimate recovery is excellent.

2. Organic causes: They account for only a small number of cases but they should be routinely excluded. Mental retardation, sacral anomalies (spina bifida, meningocele) and urological anomalies (bladder neck or urethral anomalies) are the main causes. In these cases, enuresis is commonly *severe and diurnal*.

B) SECONDARY ENURESIS

It is mostly *nocturnal* and caused by either emotional stresses or organic causes.

1. Emotional stresses: Death of a parent, birth of a new sibling, move to a new house or marital conflicts are commonly responsible for secondary enuresis. Detailed environmental history is important in every case of secondary enuresis.

2. Organic causes: Polyuria and urinary tract infection should be routinely excluded in every case of secondary nocturnal enuresis. History of dysuria or weight loss is particularly important. Urine examination should be a routine step (see also polyuria and dysuria).

6. Hypertension

Acute transient hypertension	Chronic persistent hypertension
Renal causes (most common)	**Renal causes (most common)**
Poststreptococcal glomerulonephritis	Chronic pyelonephritis (reflux nephropathy)
Nephritis of anaphylactiod purpura	Chronic glomerulonephritis
Hemolytic uremic syndrome	Chronic renal failure
Acute renal failure	Renal vascular disease
Acute pyelonephritis	Renal anomalies (dysplasia, cysts)
CNS causes	**Cardiovascular causes**
Increased intracranial pressure	Coarctation of aorta
Encephalitis	Patent ductus arteriosus
Drugs	**Other causes**
Corticosteroids, ACTH	Endocrinal hypertension
Inotropic drugs	Intracranial mass
Vitamin D intoxication	Tumors
Lead or mercury poisoning	**Essential hypertension**

Endocrinal hypertension means hyperthyroidism, hyperparathyroidism, Cushing syndrome Hyperaldosteronism or pheochromocytoma.
Renal causes account for 75 - 80% of hypertension in children.

Detection of hypertension in infants and children requires careful and accurate measurement of blood pressure. Wrong measurement is the commonest cause of hypertension in children.

1. Measurement of blood pressure

Blood pressure is indirectly measured by using a blood pressure cuff on the arm. Cuff size is particularly important because if the cuff is too wide or too narrow, false low or false high readings respectively will occur. The cuff should cover at least two-thirds of the length of the upper arm. Measurement can be made by manual or automated methods.

a) Manual measurement: The pressure in the cuff is raised above the systolic pressure (above 120 mm Hg) to occlude the brachial artery and is then lowered slowly until the return of pulsations can be detected by listening to the korotkoff sounds over the brachial artery (with a stethoscope). When the first sound is heard, the corresponding pressure is the systolic pressure. The diastolic pressure lies between the muffling and the disappearance of sounds as the cuff pressure is decreased. The measurement should be repeated once or twice for confirmation of accuracy. The return of sounds can be better detected by using a "Doppler flow detector".

b) Automated oscillometric measurement: This is a more accurate method especially in infants and young children. The first device of this kind was labeled **DINAMAP** (**D**evice for **In**direct **N**oninvasive **A**utomated **M**ean **A**rterial **P**ressure). The current models measure systolic, diastolic and MAP as well as the heart rate.

2. *Interpretation of measurements*

As arterial blood pressure increases with age, proper interpretation of measurement requires consideration of age and the normal range as well. ***Age-specific percentiles*** of BP measurements are available and can be used for interpretation. Hypertension is diagnosed with measurements above the 95th percentile for age and sex.

Systolic and diastolic Blood pressure at different ages

	Newborn	Infant	Young children	Old children
Normal mean values	80/50	80/50	85/55	90/60
Highest normal limit	90/65	100/65	110/70	120/80

According to elevation of systolic and diastolic blood pressure, 3 types of hypertension can occur.

Types of hypertension and their significance

Type	Significance
Systolic and diastolic hypertension	Renal disease
Systolic hypertension with normal diastolic pressure	Endocrinal disease
Systolic hypertension with low diastolic pressure	Cardiovascular disease

- Endocrinal hypertension is usually associated with tachycardia.

A) ACUTE TRANSIENT HYPERTENSION

Measurement of blood pressure should be an essential step in 3 clinical situations:

1. Acute renal disease: Patients presenting with hematuria, dysuria or acute renal failure are commonly having acute hypertension.

2. Acute heart failure: Measurement of blood pressure in every case of acute heart failure is essential for 2 reasons
1. Hypertension may be the cause. Some patients with poststreptococcal glomerulonephritis present clinically with hypertensive heart failure.
2. Hypotension is a sign of developing "cardiogenic shock".

3. Acute convulsions or encephalopathy: Measurement of blood pressure in every case of convulsions or encephalopathy is important:

1. Hypertension may be the cause. Some patients with poststreptococcal glomerulonephritis present clinically with convulsions and hypertensive encephalopathy and are wrongly diagnosed as intracranial infection. In this case, hypertension is usually marked.
2. Hypertension can be the indirect evidence of the increased intracranial pressure. This is particularly useful when the anterior fontanel is already closed. In this case, hypertension is usually mild to moderate.
3. Hypotension is a sign of shock or central medullary dysfunction.

Clinical presentations of acute hypertension

Headache (in older children) or irritability (in young children).
Hypertensive heart failure: Tachycardia, tachypnea and tender liver.
Hypertensive encephalopathy: Convulsions and/or disturbed consciousness.

B) CHRONIC PERSISTENT HYPERTENSION

Chronic hypertension is not uncommon in children. It is at least as common as all congenital heart diseases together. Unlike adults, more than 85% of cases are secondary to renal, endocrinal, cardiovascular or other diseases. Essential hypertension (the main cause in adults) is only diagnosed after careful exclusion of secondary causes.

Most cases of chronic hypertension in children are *"silent" or asymptomatic* and the hypertension is accidentally discovered during routine examination. When symptoms are present, *persistent or recurrent headache* is the most common. It is important to emphasize that the diagnosis of chronic hypertension should not be made except when the hypertension is persistent on repeated periodic measurements. In more than 80% of accidentally discovered hypertension, blood pressure returns to normal when examination is made few or several weeks later. This precaution is important to avoid unnecessary investigations.

Clinical evaluation of children with persistent hypertension should include the heart rate, assessment of growth, presence of anemia, cardiovascular examination including palpation of femoral pulsations and abdominal examination. Several findings may be detected and can guide the diagnosis.

Diagnostic significance of some clinical findings in chronic hypertension

Tachycardia with systolic hypertension: Endocrinal disease.
Growth failure: Chronic renal failure.
Obesity: Essential hypertension or Cushing disease.
Chronic anemia: Chronic renal failure.
Weak or absent femoral pulsations: Coarctation of aorta.
Flank abdominal masses: Cystic dysplasia, obstructive uropathy.

Several investigations are usually required to identify the cause. Essential hypertension (which is not uncommon) is only diagnosed after careful exclusion of secondary hypertension especially chronic pyelonephritis with reflex nephropathy, chronic glomerulonephritis and chronic renal diseases.

Possible investigations in children with persistent hypertension

Laboratory Investigations

Urine analysis: May reveal hematuria, proteinuria, casts or infection.
Blood urea and creatinine: Elevated in chronic renal failure.
Complete blood count: Chronic anemia with chronic renal failure.
Plasma renin activity: Elevated with renal or renovascular causes.
Urinary catecholamines: With suspected neuroblastoma or pheochromocytoma.

Imaging procedures

Abdominal ultrasound: May detect glomerular disease, obstructive lesions, neuroblastoma.
Intravenous pyelography (IVP): May reveal obstructive lesions, urinary calculi.
Voiding cystourethrography (VCUG): It is very important to exclude vesicoureteral reflux.
Doppler ultrasound and angiographic studies: With suspected renal vascular disease as stenosis, aneurysm, vascular compression or fistula.
CT scan of the head: With suspected intracranial mass.

Chronic pyelonephritis (with the resultant reflux nephropathy) is the commonest cause of chronic hypertension in children. Abdominal ultrasonography usually reveals small atrophic kidneys and the vesicoureteral reflux can be detected and graded by voiding cystourethrography.

Other renal causes especially chronic glomerulonephritis, chronic renal failure and renal vascular diseases should be excluded.

Essential hypertension should be considered in obese children. Weight reduction in these children is frequently the only required therapeutic measure.

7. Renal Failure

Acute renal failure (ARF)	Chronic renal failure (CRF)
Prerenal causes (Funtional ARF) Hypovolemia (dehydraion, hemorrhage) Hypoxemia (respiratory failure) Shock (septic, cardiogenic)	**Developmental renal anomalies** Bilateral renal hypoplasia Bilateral renal dysplasia Infantile polycystic disease Obstructive uropathy (congenital) Congenital nephrotic syndrome
Renal causes (Organic ARF) Acute glomerulonephritis Acute tubular necrosis (prerenal, drugs) Acute interstitial nephritis Hemolytic uremic syndrome Bilateral renal vein thrombosis	**Chronic glomerular diseases** Memberanoproliferative GN Systemic lupus erythematosus Hereditary nephritis
Postrenal causes (Obstructive ARF) Obstructive uropathy Congenital (stenosis, valves) Acquired (stones, clots) Functional (vesicoureteral reflux)	**Chronic urinary tract infection** Chronic pyelonephritis Bilateral vesicoureteral reflux with reflux nephropathy (important)

Episodes of **acute renal failure** may occur on top of **chronic renal failure**

Renal failure is an impairment of renal function characterized by disturbed water and electrolyte homeostasis and retention of waste products as urea and creatinine. Diagnosis of acute or chronic renal failure requires a high index of suspicion because the clinical presentations are commonly nonspecific and misleading. In acute renal failure, the clinical manifestations of the causative disease are usually the dominating features and in chronic renal failure the clinical presentations are usually not directly related to the urinary system.

A) ACUTE RENAL FAILURE

Acute renal failure is a complex clinico-laboratory syndrome caused by sudden impairment of renal function and characterized by:

1. Severe oliguria (urine output less than 1 ml/kg/hour) or anuria.
2. Acid-base and electrolyte disturbance: Metabolic acidosis, hyperkalemia, dilutional hyponatremia and hypocalcemia.
3. Retention of waste products (elevated levels of blood urea and creatinine).

Diagnosis of acute renal failure should include the diagnosis of failure and the identification of the cause.

(a) Diagnosis of acute renal failure

1. Clinical manifestations: The early manifestations of acute renal failure are usually masked or overshadowed by the clinical features of the causative disease. So, it should be suspected with any condition known to predispose to acute renal failure especially dehydration, hemorrhage, septicemia, respiratory failure, glomerulonephritis and drugs. In established and advanced cases, clinical manifestations become well evident.

Clinical staging of acute renal failure

Early acute renal failure
Clinical manifestations of the cause are the dominating features.
Oliguria and weight gain may be observed.

Established acute renal failure
Severe oliguria or anuria (accurate urine output is important).
Edema and hypertension. Pallor (anemia) may be also evident.
Acidotic breathing: Deep rapid respiration due to metabolic acidosis.

Advanced acute renal failure
Congestive heart failure and pulmonary edema (due to volume overload).
Cardiac arrhythmias (due to severe hyperkalemia).
Convulsions (due to severe hypocalcemia or hyponatremia).
Coma or uremic encephalopathy (due to severe acidosis, marked uremia).
Gastrointestinal bleeding (due to stress ulcers and platelet dysfunction).

- It is important to emphasize that acute renal failure may occur without oliguria especially with nephrotoxic drugs (nonoliguric acute renal failure). So, estimation of renal function is important with prolonged use of nephrotoxic drugs (as aminoglycosides and potent diuretics).

2. Laboratory diagnosis: With clinical suspicion of acute renal failure, laboratory investigations are essential to confirm the diagnosis. Blood urea and serum creatinine, blood gases (for acid-base balance) and serum electrolytes (K, Na, Ca, Ph) are the most relevant investigations. Other diagnostic procedures as chest x-ray (pulmonary edema) and ECG (arrhythmias) may be also indicated.

Laboratory diagnosis of acute renal failure

Elevated levels of bood urea (above 50 mg/dl) and serum creatinine (above 2 mg/dl).
Metabolic acidosis (low pH, low HCO3 and low $PaCO_2$).
Electrolyte disturbance: Hyperkalemia, hyperphosphatemia, hypocalcemia, hyponatremia.

(b) Diagnosis of the cause

1. Clinical manifestations: With ***prerenal causes,*** clinical manifestations of the causative disease are usually well evident as dehydration, hemorrhage, respiratory failure or shock. With ***renal causes,*** hematuria (glomerulonephritis), purpura

(hemolytic uremic syndrome, renal vein thrombosis), acute hemolytic anemia (hemolytic uremic syndrome, renal vein thrombosis) and flank masses (renal vein thrombosis, cystic disease or tumours) are the most relevant clinical findings. ***Postrenal causes*** should be considered in presence of flank masses.

2. Diagnostic procedures: Several investigations are usually needed to identity the cause especially with renal and postrenal causes. CBC, CRP, urine analysis and culture and abdominal ultrasound are the essential initial procedures.

Diagnostic significance of laboratory and imaging abnormalities

Leukocytosis and elevated CRP: Septicemia, lupus nephritis.
Acute hemolytic anemia: Hemolytic uremic syndrome, renal vein thrombosis, septicemia.
Thrombocytopenia: Hemolytic uremic syndrome, renal vein thrombosis, septicemia.
Gross hematuria: Glomerulonephritis, renal vein thrombosis.
Renal masses by ultrasound: Renal vein thrombosis, obstructive uropathy, tumours, cystic disease.
Low serum complement 3: Glomerulonephritis (poststreptococcal, lupus).

Finally, it is important to remember that infections and drugs can cause acute renal failure through several mechanisms

Role of infections and drugs in acute renal failure

Infection-associated acute renal failure

Septicemia: Septic shock (prerenal) and interstitial nephritis (renal).
Severe gastroenteritis: Dehydration (prerenal), may be followed by hemolytic uremic syndrome or renal vein thrombosis.
Urinary tract infection: Pyelonephritis (interstitial nephritis), precipitation of acute episode in obstructive and chronic renal failure.

Drug-associated acute renal failure

Nephrotoxic drugs: Acute tubular necrosis.
Antibiotics, nonsteroidal anti-inflammatory drugs: Interstitial nephritis.

• Antibiotics that may cause acute interstitial nephritis include penicillins, cephalosporins, co-trimoxazole and rifampicin. **Acute interstitial nephritis** should be suspected in presence of fever, maculopapular rash and eosinophilia.

B) CHRONIC RENAL FAILURE

Chronic renal failure occurs with conditions that cause permanent destruction of functioning nephrons and permanent reduction of glomerular filtration rate. Clinical manifestations of renal insufficiency do not appear until glomerular filtration rate is below 20 - 30 ml/minute/m2 (normal value is 70 ml/minute/m2). Once a critical level of renal functional deterioration is reached, progression to end-stage renal disease (ESRD) will occur.

Diagnosis of chronic renal failure requires a high index of suspicion because clinical presentations are usually nonspecific and not directly related to urinary symptoms. It is also important to know that CRF may present for the first time with an episode of ARF.

Clinical presentations of chronic renal failure

Chronic vomiting and failure to thrive (see chronic vomiting).
Chronic unexplained anemia (see chronic anemia).
Chronic persistent hypertension (see hypertension).
Growth failure.
Rickets above the age of 4 years (renal osteodystrophy).
Polyuria and polydipsia.

- With any of the above presentations, evaluation of renal function and abdominal ultrasound are essential to exclude chronic renal failure.
- Also in patients presenting with acute renal failure, periodic evaluation of renal function after recovery is important because ARF can be the initial presentation of chronic renal failure.

Laboratory diagnosis of chronic renal failure

Persistent elevation of blood urea and serum creatinine levels.
Chronic metabolic acidosis.
Hyperphosphatemia and hypocalcemia. Potassium may be normal, low or high.
Reduction of glomerular filtration rate (below 20 - 30 ml/minute/m^2).

- **Calculation of glomerular filtration rate:** A simple method for calculation depends on the length of the patient and the serum creatinine level where:

  Glomerular filtration rate (GFR) = 0.5 (length)/serum creatinine.

- **The cause of CRF** can be identified with abdominal ultrasound, CT scan and renal biopsy. Developmental anomalies and reflux nephropathy (see urinary tract infection) are the main causes.
- **Developmental renal diseases** are the main causes in children below the age of 5 years. The anomalies are classified as following:

  a) Anomalies in amount of renal tissue
  Renal agenesis (unilateral or bilateral).
  Renal hypoplasia (unilateral or bilateral).

  b) Anomalies in renal differentiation
  Renal dysplasia (unilateral or bilateral).
  Polycystic kidney disease (infantile type and adult type).

  c) Anomalies in location and shape of the kidney
  Renal ectopia
  Horseshoe kidney.

  d) Congenital obstructive lesions in collecting system, bladder and urethra
  Hydronephrosis, hydroureter, ureterocele.
  Posterior urethral valve, vesicoureteral reflux (2 important causes of obstructive uropathy).

- Only the bilateral anomalies can lead to CRF as bilateral renal hypoplasia, bilateral renal dysplasia and infantile type of polycystic kidney disease. Bilateral renal agenesis (Potter syndrome) is rapidly fatal in neonatal period.

- **Small kidney** by ultrasound is caused by renal hypoplasia, renal dysplasia, atrophic kidney (following vesicuoreteral reflux and pyelonephritis) and renal vascular insult in infancy.

10

Hematology

1. Anemias.
2. Purpura.
3. Coagulation Disorders.

1. Anemias

Acute anemias	Chronic anemias
Acute blood loss	**Microcytic anemias**
Traumatic bleeding	Iron deficiency anemia
Surgical bleeding	Thalassemias
Gastrointestinal bleeding	Sideroblastic anemia
Bleeding disorders	Lead poisoning
Purpuras	**Normocytic anemias**
Coagulation dosorder	Chronic hemolytic anemias
Acute hemolytic anemias	Chronic renal failure
Hemolytic crisis of G6PD deficiency	Chronic infection or inflammation
Crises of chronic hemolytic anemias	Bone marrow replacement
Hemolytic uremic syndrome	**Macrocytic anemias**
Hemolytic anemia of infection	Hypoplastic (pure red cell) anemia
Acute autoimmune hemolytic anemia	Aplastic pancytopenia
Metabolic hemolytic anemia	Megaloplastic anemias
Erythrocytic porphyria	Immune hemolytic anemia
Wilson disease	

Anemia is a very common clinical presentation in pediatric practice. It is defined as a "reduction in the number of circulating red cells with the resultant decrease in hemoglobin level". It is important to remember that the normal hemoglobin level is different at different age groups and diagnosis of anemia is only made with hemoglobin levels below the normal range for age.

Normal hemoglobin and mean corpuscular volume (MCV) at different ages

	Newborn	Infant	Young children	Old children
Hemoglobin	16 gm/dl (13-20)	12 gm/dl (10-14)	12 gm/dl (10-14)	13 gm/dl (11-15)
MCV	100-110	70-74	70-74	76-80

Anemia can be mild, moderate, severe or profound according to the degree of lowering of hemoglobin level. ***Pallor*** is the main clinical presentation.

Degrees of anemia in infants and young children

	Mild	Moderate	Severe	Profound
Hemoglobin level	8-10 gm/dl	6-8 gm/dl	4-6 gm/dl	below 4 gm/dl

A) ACUTE ANEMIAS

In acute anemias, the history is very short (hours or days) and the patient looks acutely ill with pallor and features of acute hypoxia (as tachycardia, rapid respiration and altered consciousness) especially in severe cases.

(a) Acute blood loss

With acute anemia due to acute blood loss, the cause and the source of bleeding are usually well evident (trauma, surgery or gastrointestinal bleeding). The major risk or complication in severe cases is the development of hypovolemic shock and hypoxic anemic encephalopathy.

The most important step in clinical evaluation is how to assess the severity of the condition or, in other words, how to estimate the volume of blood loss. The degree of pallor and the clinical effects of blood loss can provide a useful guidance.

Clinical assessment of the acute blood volume loss

Class I: 15% or less acute blood volume loss
Tachycardia only

Class II: 20-25% acute blood volume loss
Tachycardia (above 150 beats/minute)
Tachypnea (above 40 breath/minute)
Prolonged capillary refill and hypotension

(Hypovolemic shock)

Class III: 30-35% acute blood volume loss
All above signs
Disturbed consciousness (lethargy, confusion).
Oliguria (urine output less than 1 ml/kg/hour)

Class IV: 40-50% acute blood volume loss
No palpable pulse
Coma (due to severe hypovolemic shock and hypoxic anemic encephalopathy)

- **Urgent whole blood transfusion** is indicated in class II, III and VI. The given volume depends on the estimated blood volume loss (20 ml/kg in class II, 30 ml/kg in class III and 40 ml/kg in class IV). In case of ongoing blood loss, blood transfusion can be repeated as frequent as necessary.
- **Local measures** to control bleeding are equally important.
- **Oxygen therapy and volume expanders** (as Ringer's lactate) should be given until blood becomes available for transfusion.

(b) Acute hemolytic anemias

Acute hemolysis is a condition characterized by rapid destruction of red cells in peripheral blood leading to acute anemia, unconjugated hyperbilirubinemia and hemoglobinuria. Rapid and accurate diagnosis is important because in most cases, urgent red cell transfusion is necessary and could be life-saving.

Clinical and laboratory diagnosis of acute hemolysis

Clinical manifestations

Acute intense pallor (due to acute hemolysis).
Acute jaundice (due to unconjugated hyperbilirubinemia)
Dark urine, pink to red (due to hemoglobinuria)
Manifestations of acute hypoxia (tachycardia, tachypnea and coma) in severe cases.
Fever may be also present.

Laboratory confirmation

Acute anemia with fragmented or distorted red cells.
Reticulocytosis (above 5%) except with aplastic crisis (reticulocytopenia).
Unconjugated hyperbilirubinemia.
Hemoglobinemia and hemoglobinuria.

- **Acute hemolysis** should not be confused with **acute hepatitis** as in both conditions, acute jaundice and dark urine are present. In acute hemolysis, intense pallor is the most prominent feature, which is absent with acute hepatitis (see also acute jaundice and dark urine).
- Whatever the cause, **Urgent red cell transfusion** (10 ml/kg) is necessary.

Identification of the cause of hemolysis requires careful clinical examination and some laboratory investigations. Clinical examination should include a search for purpura (hemolytic uremic syndrome or septicemia), splenomegaly (crisis of chronic hemolytic anemia or acute autoimmune hemolytic anemia) and manifestations of acute renal failure (hemolytic uremic syndrome). History of exposure to drugs (G6PD deficiency) and evaluation of the general condition (bad with septicemia) are also important. Laboratory investigations are usually chosen according to the most likely clinical diagnosis.

Possible laboratory investigations with acute hemolysis

CBC and CRP: In all cases (especially with suspected septicemia).
Evaluation of renal function: With suspected hemolytic uremic syndrome.
Coomb's test: With suspected autoimmune hemolytic anemia.
G6PD enzyme activity (3 weeks after the acute episode): With suspected G6PD deficiency.
Laboratory investigations of chronic hemolytic anemias.
Other investigations as blood film (for malaria) and serum ceruloplasmin (for Wilson disease).

The main causes of acute hemolytic anemias are:

1. Hemolytic crisis of G6PD deficiency: Glucose 6 phosphate dehydrogenase (G6PD) deficiency is an x-linked disease common in Mediterranean areas and is characterized by marked deficiency of the G6PD enzyme activity inside the red cells (about 5-10% of normal activity). Normally, the enzyme is responsible for the physiological protection of hemoglobin from oxidation on exposure to oxidant materials. With its deficiency, exposure to oxidant materials results in oxidation of hemoglobin to methemoglobin and its precipitation inside the red cells to form Heinz bodies. These red cells will be rapidly removed from the circulation leading to acute anemia.

• Acute hemolytic crisis occurs on exposure to oxidant materials especially certain drugs and foods. Infections also (bacterial or viral) may induce hemolysis in some patients.

• Diagnosis is confirmed by the presence of the markedly reduced G6PD enzyme activity below 20 unit/10^{12} RBC (normal value is above 100 unit/10^{12} RBC). Estimation of G6PD enzymatic activity should be made after 3 weeks of acute hemolysis because immediately after hemolysis, the bone marrow releases immature forms of red cells with a higher enzymatic activity and a false normal results may be obtained.

Drugs and foods that induce hemolysis in G6PD deficiency

Drugs: Antipyretics as acetylsalicylic acid (aspirin) and metamizole (novalgin).
Antibiotics as chloramphenicol, nalidixic acid and furazolidone.
Sulphonamides (several antidiarrheal preparations contain sulphonamides).
Antimalarial drugs.

Foods: Broad beans and its products are the most potent oxidants.
Fava bean (Favism) is also a potent oxidant.
Other beans as greens beans and peas may be also responsible.

• In Egypt, the condition is usually discovered in late infancy as an acute hemolytic episode following ingestion of broad beans.

2. Crises of chronic hemolytic anemias: Several crises may occur in patients with chronic hemolytic anemias especially in response to infections.

a) Aplastic crisis: It is a transient episode of acute bone marrow failure, which usually occurs in response to infection. It leads to a severe and rapid life-threatening anemia because the shortened survival time of red cells in no longer compensated. It is a self-limited attack, which usually lasts 10-14 days. Diagnosis depends on the presence of acute severe anemia and reticulocytopenia (not reticulocytosis) in a known case of chronic hemolytic anemia. Bone marrow examination reveals diminished red cell precursors. Aplastic crisis of chronic hemolytic anemia should not be confused with aplastic anemia. Aplastic crisis is an acute anemia because it occurs in a hyperactive bone marrow of chronic hemolytic anemia while aplastic anemia is a chronic anemia because it occurs in a normal bone marrow.

b) Hyperhemolytic crisis: It is characterized by acute hemolytic episode with intense pallor, jaundice and dark urine (hemoglobinuria). Reticulocytic count is high (important differentiating point from aplastic crisis).

c) Sequestration crisis: It is an acute severe anemia caused by sudden pooling of large amount of blood into the liver and spleen. Clinically, liver and spleen are markedly enlarged and may be tender, and manifestations of hypovolemic shock may be evident. Although sequestration crisis is not a hemolytic crisis, it should be considered in patients of chronic hemolytic anemia presenting with acute anemia.

d) Vaso-occlusive (painful) crisis: It is characterized by painful swellings of hands and feet (hand-foot syndrome) and painful swellings of large joints (see arthritis). It occurs

mainly in sickle cell anemia. It is not associated with acute anemia but only mentioned here to be compared with other crises.

3. Hemolytic uremic syndrome: It is a syndrome of acute hemolytic anemia, acute renal failure, thrombocytopenia and distorted red cells. Clinically, acute intense pallor, hematuria, oliguria and purpura are usually present. Laboratory diagnosis depends on the presence of acute hemolysis, distorted red cells, thrombocytopenia and acute renal failure. The conditions should be differentiated from bilateral renal vein thrombosis and septicemia because in these 3 conditions acute hemolysis, acute renal failure and thrombocytopenia may coexist (see hematuria and acute renal failure).

4. Hemolytic anemia of infections: Certain infections especially ***septicemia*** and ***malaria*** can produce direct destruction of the red cells by the organisms or their toxins. In these conditions, in addition to acute hemolysis, the clinical manifestations of the cause are usually evident. With septicemia, the patient is critically sick and thrombocytopenia and acute renal failure may also occur. Clinical and laboratory differentiation from hemolytic uremic syndrome and bilateral renal vein thrombosis is important. It is also important to remember that infections can also precipitate hemolysis in patients with G6PD deficiency or chronic hemolytic anemia.

5. Acute autoimmune hemolytic anemia: It occurs due to presence of abnormal antibodies produced by the patient and directed against his red cells. The illness is commonly preceded by a respiratory infection. Clinically, manifestations of acute hemolysis (intense pallor, jaundice, dark urine and may be fever) and marked splenomegaly are usually evident. Laboratory findings are characteristic and include marked reticulocytosis (about 50% of circulating red cells), spherocytosis, leukocytosis and strongly positive direct Coomb's test. Concomitant immune thrombocytopenia may be occasionally present (Evans syndrome). The illness responds to steroids and full recovery usually occurs within few months except in Evans syndrome where the condition may become chronic (i.e. thrombocytopenia is a bad prognostic sign).

6. Metabolic acute hemolysis: Rarely, acute hemolytic anemia can be caused by metabolic diseases especially erythrocytic porphyria and Wilson disease. When acute hemolysis and acute hepatitis coexist, Wilson disease should be always excluded.

B) CHRONIC ANEMIAS

In chronic anemias, the history is rather long (weeks to months) and the patient does not look acutely ill (no signs of acute hypoxia). Clinical signs of anemia depend on its degree.

Signs of chronic anemia

Mild to moderate anemia: Pallor is the only sign.
Moderate to severe anemia: Hemic systolic murmur over the pulmonary area.
Severe to profound anemia: Anemic heart failure may occur.

In chronic anemias, accurate clinical diagnosis can never be made and some investigations are always necessary to reach the diagnosis. However, clinical examination is very useful to put some possibilities forward.

Diagnostic significance of some clinical signs in chronic anemia

Jaundice and splenomegaly or hepatosplenomegaly: Chronic hemolytic anemia.
Hepatosplenomegaly (without jaundice): Leukemia, chronic infection.
Purpura or bleeding: Leukemia, aplastic anemia, immune hemolytic anemia.
Arthritis: Leukemia, chronic infection or inflammation.
Skeletal anomalies (as microcephaly, absent radius or thumb): Fanconi anemia.
Skeletal changes (large head, prominent maxillae): Chronic hemolytic anemia.
Growth failure with chronic vomiting: Chronic renal failure.
Pallor only (no other signs): Iron deficiency, hypoplastic (pure red cell) anemia.

Initial laboratory investigations should include complete blood count, reticulocytic count, serum iron and iron binding capacity. Further investigations are indicated when initial investigations are inconclusive and they include investigations for chronic hemolysis, evaluation of renal function and bone marrow examination.

Diagnostic significance of laboratory investigations in chronic anemia

Type of anemia (Microcytic. mornocytic or macrocytic) by mean corpuscular volume (MCV).
Reticulocytosis (above 2%): Chronic hemolytic anemia, iron deficiency with therapy.
Blast cells in peripheral blood: Acute leukemia.
Thrombocytopenia: Leukemia, aplastic anemia, immune hemolytic anemia.
Low serum iron with high iron binding capacity: Iron deficiency anemia.
Low serum iron with normal iron binding capacity: Chronic infection, chronic renal failure.
High serum iron with low iron binding capacity: Chronic hemolytic anemia.
Elevated blood urea and creatinine: Chronic renal failure.
Bone marrow examination:

- Erythroid hyperplasia: Iron deficiency anemia, chronic hemolytic anemia.
- Megaloblastic changes: Megaloblastic anemias.
- Hypoplastic bone marrow: Hypoplastic anemia (pure red cell anemia).
- Aplastic bone marrow: Aplastic anemia.
- Abnormal cells: Leukemia, lymphoma, neuroblastoma, Gaucher cells, ringed sideroblasts (sideroblastic anemia).

The following discussion is based on the type of anemia (microcytic, normocytic and macrocytic). These morphological changes are best studied by determination of mean corpuscular volume (MCV). The normal mean corpuscular volume in infants and children is between 75-95 fl.

Mean corpuscular volume in anemias

Microcytic (below 75 fl). **Normocytic** (75-95 fl). **Macrocytic** (above 100 fl).

Other *morphological changes* of red cells are also important and can help in diagnosis. The most important morphological changes are those of severe iron deficiency anemia (anisocytosis, poikilocytosis) and some chronic hemolytic anemias (spherocytosis, elliptocytosis or sickle cells).

(a) Microcytic anemias

1. Iron deficiency anemia: It is by far the most common cause of anemia in pediatric age group. The condition should be suspected in every case of prolonged breast-feeding, chronic diarrhea or repeated blood loss.

• ***Clinically***, the onset is usually above the age of 9 months. In addition to pallor, anorexia and pica (diverted appetite to wall paints, mud) may be prominent. In severe longstanding cases, splenomegaly and skeletal changes similar to those of chronic hemolytic anemia may be also present.

• ***Laboratory diagnosis*** depends on the presence of:

1. Hypochromic microcytic anemia. Anisocytosis and poikilocytosis are also present in severe cases. Transient increase in reticulocytic count occurs with initiation of iron therapy (this transient reticulocytosis with rising hemoglobin level should not be confused with the persistent reticulocytosis and steady hemoglobin level that occurs in chronic hemolytic anemia).

2. Low serum iron below 50 mcg/dl (normal level is 90 - 150 mcg/dl) and high iron binding capacity above 350 mcg/dl (normal level is 250 -350 mcg/dl). Serum ferritin, if available, is also an early sensitive test. It is usually below 10 ng/ml (normal level is about 35 ng/ml).

3. Bone marrow examination reveals erythroid hyperplasia. However, it is not necessary and not indicated in most cases.

2. Thalassemias: In ***beta thalassemia major*** (Cooley's anemia), the clinical triad of anemia, jaundice and splenomegaly is well evident and the laboratory manifestations of chronic hemolysis in addition to the markedly elevated hemoglobin F make no diagnostic difficulty. In ***beta thalassemia minor*** (thalassemia trait), the anemia is usually mild and the condition should be suspected in every case of hypochromic microcytic anemia not responding to iron therapy. Diagnosis is established by hemoglobin electrophoresis, which reveals the characteristic elevation of hemoglobin A_2 above 4% (normal level is below 2%). ***Alpha thalassemia trait*** should be considered if hemoglobin A_2 is not elevated.

3. Sideroblastic anemia: It is a hypochromic microcytic anemia due to abnormalities of iron or heme metabolism. The condition should be also suspected in every case of hypochromic microcytic anemia not responding to iron therapy. Serum iron is elevated and bone marrow examination reveals the characteristic ringed sideroblasts (nucleated red cells with a perinuclear collar of coarse hemosiderin granules). Some cases of sideroblastic anemia may respond to pyridoxine (vitamin B6) therapy.

4. Lead poisoning: Chronic lead poisoning occurs with environmental exposure to lead in food, drinking water and air. Clinical manifestations are usually vague and nonspecific but the condition should be considered in the differential diagnosis of hypochromic microcytic anemia, severe behavioural disorders, school underachievement and mental retardation. In hypochromic microcytic anemia due to lead poisoning, there is a prominent coarse basophilic stippling of the red cells. Blood lead level is markedly elevated above 60 mcg/dl (normal level is below 20 mcg/dl).

(b) Normocytic anemias

1. Chronic hemolytic anemias: The clinical triad of chronic anemia, mild jaundice and splenomegaly (or hepatosplenomegaly) is characteristic of chronic hemolytic anemia. Positive family history and history of repeated transfusions may be obtained. Growth failure and skeletal changes (large head, prominent maxillae, mongoloid features) may be prominent especially in severe cases of Cooley's anemia. Other hematological findings as purpura or bleeding are usually absent except when complicated with hypersplenism. Most inherited conditions present in late infancy and early childhood. Acquired chronic autoimmune hemolytic anemia can be primary or secondary to other diseases as systemic lupus erythematosus or lymphomas. Laboratory diagnosis should include diagnosis of chronic hemolysis and diagnosis of the cause.

Laboratory diagnosis of chronic hemolytic anemias

Diagnosis of chronic hemolysis

- Chronic anemia: Usually normocytic except in thalassemias (microcytic).
- Sustained reticulocytosis above 2%.
- High serum iron (above 150 mcg/dl) and low iron binding capacity.
- Mild unconjugated hyperbilirubinemia.
- Hyperactive bone marrow (not routinely required).

Diagnosis of the cause

- Morphological study of red cells: Congenital spherocytosis, elliptocytosis.
- Enzymatic study of red cells: G6PD or pyruvate kinase deficiency.
- Hemoglobin electrophoresis: Hemoglobinopathies.
- Coomb's test: Highly positive in chronic autoimmune hemolytic anemia.
- Other tests: Osmotic fragility test (increased in congenital spherocytosis).
  Heat stability test (for detection of unstable hemoglobins).

• Reticulocytosis above 10% is not unusual. In autoimmune hemolytic anemia, reticulocytic count is usually above 20% and may even reach 50%.

Hemoglobin electrophoresis is essential for diagnosis and differentiation between different types of hemoglobinopathies. However, normal hemoglobin electrophoresis does not exclude the possibility of hemoglobinopathies as some conditions (unstable hemoglobins) need special tests for diagnosis (heat stability test).

Diagnosis of hemoglobinopathies by hemoglobin electrophoresis

	Hb A	Hb A_2	Hb F	Hb S	Hb C
Normal values	98%	2%	2%	—	—
Thalassemia major	50%	2%	50%	—	—
Thalassemia minor	90%	5%	5%	—	—
Sickle cell anemia	Absent	—	10%	90%	—
Sickle cell trait	65%		—	35%	
Hb S-thalassemia	20%	—	10%	70%	—
Hb S-C disease	—	—	10%	45%	45%

- Hb F above 50% is diagnostic of thalassemia major (Cooleys anemia).
- Hb A_2 above 4% is diagnostic of thalassemia minor (thalassemia trait).
- Thalassemia intermedia (Hb H disease) is diagnosed by detection of Hb H (4 - 20%).
- Hb S above 90% is diagnostic of sickle cell anemia (Hb A is absent).
- Hb S about 70% is usually due to Hb S thalassemia (Hb A is present).
- Hb S about 45% is usually due to Hb S-C or Hb S-D disease.
- HbS about 35% is usually due to sickle cell trait (HbA is 65%).
- Elevation of hemoglobin F is not peculiar to hemoglobinopathies but it also occurs with aplastic anemia and hereditary persistence of fetal hembglobin (HPFH).

2. Chronic renal failure: The possibility of chronic renal failure should be considered in every case of longstanding unexplained anemia. Other nonspecific manifestations as growth failure and chronic vomiting may be also present. As hypertension is commonly present, blood pressure should be routinely measured in cases of unexplained anemia in children. The anemia is usually normocytic. Serum iron is low but iron binding capacity is normal. Diagnosis is confirmed by elevated levels of blood urea and serum creatinine (see renal failure).

3. Chronic infection or inflammation: In these conditions, the clinical manifestations of the cause are usually the dominating features (see prolonged fever). Anemia is similar to that of chronic renal failure (normocytic with low serum iron and normal iron binding capacity).

4. Bone marrow replacement or infiltration: The conditions causing bone marrow replacement or infiltration include common malignancies (leukemia, lymphoma, neuroblastoma), metabolic diseases (as Gaucher disease) and other rare hematological diseases (as myelofibrosis). In these conditions, anemia is usually associated with thrombocytopenia and may be leukopenia (pancytopenia). Diagnosis is usually suggested by the characteristic clinical manifestations and confirmed by bone marrow examination.

(c) Macrocytic anemias

1. Hypoplastic anemia (pure red cell anemia): It occurs due to selective hypoplasia of red cell precursors in the bone marrow. It is also called "pure red cell

anemia" because the granulocytic and megakaryocytic series in the bone marrow are normal. The possibility of hypoplastic anemia should be considered when clinical examination does not reveal any other findings. Laboratory diagnosis depends on the presence of (1) Macrocytic anemia, (2) Reticulocytopenia (decreased reticulocytic count to less than 0.1%) and (3) Diminished red cell precursors in the bone marrow with normal granulocytic series and megakaryocytes. There are 2 types; congenital and acquired:

a) Congenital pure red cell anemia (Blackfan Diamond anemia): The onset is in early infancy and the anemia becomes severe and evident at the age of 2 - 4 months. The anemia is persistent and repeated blood transfusions are usually necessary. Unless corticosteroid therapy produces remission, death will eventually occur from chronic congestive heart failure.

b) Acquired pure red cell anemia: It may occur at any age and it can be transient or persistent. History of preceding viral infection or drug administration (as chloramphenicol) may be obtained in some cases. The anemia following viral infections is usually transient and benign.

2. Aplastic anemia (aplastic pancytopenia): It occurs due to aplasia of the precursors of the 3 blood elements in the bone marrow leading to pancytopenia. The possibility of aplastic pancytopenia should be considered when purpura or bleeding precedes the onset of anemia. Clinically, anemia and purpura are the only findings. Splenomegaly and lymphadenopathy are absent (important differentiating point from acute leukemia). Laboratory diagnosis depends on the presence of pancytopenia (anaemia, leukopenia and thrombocytopenia) and aplastic bone marrow (hypocellular with depressed precursors of the 3 blood elements). There are 2 types of aplastic anemia; congenital and acquired:

a) Congenital or constitutional aplastic pancytopenia (Fanconi anemia): It is an autosomal recessive disease. About 50% of cases have skeletal anomalies as microcephaly, absent radius, absent thumb and short stature. Other anomalies as microphthalmia and generalized hyperpigmentation may be also present. The onset of hematological changes is usually above the age of 3 years (2 -20 years) with an average of 6 - 8 years. Thrombocytopenia appears first, followed by progressive severe anemia and leukopenia. Progression is usually slow and survival for several years is the rule. Fanconi anemia should not be confused with Fanconi syndrome (see rickets).

b) Acquired aplastic pancytopenia The history is relatively short (several weeks) and history of preceding infection (as hepatitis) or drug administration (as chloramphenicol) is present in 50% of cases.

The prognosis of aplastic pancytopenia is generally poor. In the congenital form (Fanconi anemia), survival for many years can be achieved by androgen and corticosteroid therapy, but ultimately death from infections or uncontrolled bleeding will occur. In the acquired form, the prognosis is worse and 70% of cases will die within 6 months of onset. Even in the lucky 10 - 20% of cases who recover, acute leukemia may develop. However, recently, bone marrow transplantation offers a 90% chance of long-term survival.

3. Megaloblastic anemia: It occurs with folic acid deficiency (common) or B12 deficiency (rare). ***Folic acid deficiency*** should be considered in presence of chronic diarrhea, malnutrition or in infants receiving goat's milk. It should be also considered as an associated anemia in patients with chronic hemolytic anemia. ***Vitamin B_{12} deficiency*** should be considered in presence of neurological manifestations as ataxia or positive Babiniski sign.

Laboratory diagnosis of megaloblastic anemia

Peripheral blood

Macrocytic anemia.
Platelets and white cells may be also reduced (pancytopenia).
Hypersegmented neurophils (shift to right) is a common finding.

Bone marrow

Hyperactive bone marrow with megaloblastic changes.
Giant metamyelocytes.
Hypersegmented nuclei of megakaryocytes.

- Serum folic acid is low in folic acid deficiency (less than 3 ng/ml).
- Serum B_{12} is low in B_{12} deficiency (less than 100 pg/ml).

2. Purpura

Acute purpura	Chronic purpura
With good general condition	**with aplastic bone marrow**
Idiopathic thrombocytopenic purpura	Aplastic pancytopenia
Henoch-Schonlein purpura	Hypoplastic thrombocytopenia
Drug-induced purpura	Acute leukemia
Traumatic purpura	Bone marrow replacement
With bad general condition	**with normal bone marrow**
Disseminated intravascular coagulation	Wiskott-Aldrich syndrome
Hemolytic uremic syndrome	Hypersplenism
Bilateral renal vein thrombosis	Immune pancytopenia
Severe septicemia	Megaloplastic anemias

Purpura is a small hemorrhage into the superficial layers of the skin and mucous membranes that produces areas of purple discoloration, which do not blanch on pressure.

• **Size of purpuric lesions:** Minute spots of 1- 2 mm in diameter are known as *"petechiae or petechial spots"*. Larger areas of 1- 2 cm in diameter are known as *"ecchymoses or ecchymotic patches"*. Petechiae are commoner than ecchymoses but both lesions are frequently present together. When large ecchymotic patches are the only lesions, traumatic purpura or coagulation disorders should be considered.

• **Distribution of purpuric lesions:** In most cases, the *skin of the trunk* is the most commonly involved area but limbs and face may be also affected. The distribution is usually random and nonspecific except in Henoch-Schoenlein purpura (characteristic rash over the buttocks and back of lower limbs) and traumatic purpura (face and limbs are the main sites).

• **Bleeding** is the main complication and it can be mild or severe. Bleeding from the *mucous membranes* of the mouth (bleeding gums) or nose (epistaxis) is the most common. Internal hemorrhage especially intracranial hemorrhage is a serious rare complication. When anemia (pallor) is clinically evident it is important to know whether it is due to acute blood loss or related to the underlying disease. Anemia is a common associated finding in most cases of chronic purpura (see below).

Classifications

Purpura can be classified in different ways:

- ***Clinically,*** it is classified into acute and chronic.
- ***Hematologically,*** it is classified into thrombocytopenic and nonthrombocytopenic.

Both classifications are clinically and diagnostically useful:

Hematological classification of purpura

Thrombocytopenic purpura

The number of circulating platelets is reduced.

It is further divided into 2 groups according to the number of megakaryocytes in bone marrow:

a) Normomegakaryocytic

The mechanism of thrombocytopenia is the peripheral destruction of the circulating platelets.

It can be acute or chronic.

- ***Acute:*** Idiopathic thrombocytopenic purpura (commonest).
  Disseminated intravascular coagulation.
  Hemolytic uremic syndrome.
  Bilateral renal vein thrombosis.
  Severe septicemia.
- ***Chronic:*** Wiskott-Aldrich syndrome (x-linked disease).
  Hypersplenism.
  Immune pancytopenia.
  Megaloblastic anemias.

b) Hypomegakaryocytic

The mechanism of thrombocytopenia is the decreased number of megakaryocytes in the bone marrow.

It is always ***chronic***

Aplastic pancytopenia.
Hypoplastic thrombocytopenia.
Acute leukemia.
Bone marrow replacement.

Nonthrombocytopenic purpura

The number of circulating platelets is normal.

The mechanism is either vascular (increased capillary fragility) or platelet dysfunction.

a) Vascular purpura

Henoch-Schoenlein purpura.
Traumatic purpura.
Acute infections (viral or bacterial).

b) Platelet dysfunction

Drug-induced purpura.
Renal failure (uremia).
Hepatic failure (cholemia).

A) ACUTE PURPURA

In acute purpura, the onset is ***abrupt*** and the whole duration of illness is generally short (usually one or 2 weeks). Clinical distinction between different causes is not very difficult. Platelet count is the essential initial laboratory investigation. Bone marrow examination is not indicated except when the illness persists for more than 3 weeks.

Evaluation of the general condition (see short febrile illness) is very important for classification of patients into 2 groups (with good or with bad general condition).

(a) Acute purpura with good general condition

1. Idiopathic thrombocytopenia purpura (ITP): It is the most common cause of purpura in children. The illness is mostly immune in origin (platelet antibodies may be detected) and it is often preceded by a viral infection 1 - 4 weeks before the onset of purpura.

• The onset is abrupt with purpura and may be bleeding. Epistaxis can be severe but intracranial hemorrhage is rare. Apart from the purpura and bleeding, the patient appears clinically well with no other clinical findings. Anemia, if present, is related to blood loss.

• Laboratory diagnosis depends on the presence of severe thrombocytopenia (platelet count is usually below 20.000). Bone marrow examination is not indicated except when purpura persists for more than 3 weeks. Bone marrow examination reveals a normal or increased number of megakaryocytes.

• Prognosis is excellent in most cases. Purpura and bleeding usually subside over 1-2 weeks but thrombocytopenia may persist longer. In some patients, thrombocytopenia may persist for several months or may even become chronic (thrombocytopenia for more than 1 year).

2. Henoch-Schoenlein purpura: It is a vasculitis syndrome characterized by nonthrombocytopenic purpura, arthritis, abdominal pain and nephritis. ***Characteristic skin lesion*** is a purpuric rash involving mainly the back of lower limbs and buttocks but it may extend to involve the trunk and upper limbs. ***Arthritis*** occurs in two thirds of cases, affecting few large joints and remains for only few days. ***Gastrointestinal manifestations*** occur in 50%of cases. Colicky abdominal pain is the main feature and it may be associated with gastrointestinal hemorrhage (bleeding per rectum and may be hematemesis). ***Nephritis*** occurs in one third of cases and it may appear during the acute stage or few weeks after recovery. It is usually not severe, only manifesting with hematuria with or without casts and proteinuria. It usually subsides completely over few weeks but chronic renal failure may occur. ***Neurological manifestations*** as convulsions, coma and paralysis are rare but serious complications. Prognosis is generally excellent and most cases recover completely over few days or few weeks. There are no specific laboratory findings and the diagnosis is clinical.

3. Drug-induced purpura: History of drug administration should be taken in every case of acute purpura. Drugs as aspirin, sulphonamides and antihistamines may be responsible. The mechanism is either thrombocytopenic, platelet dysfunction or vascular. The purpuric eruption has no characteristic distribution. The patient appears clinically well and the condition subsides with discontinuation of the offending drug.

4. Traumatic purpura: It is probably the most common cause of all purpuras. The trauma can be accidental or nonaccidental (child abuse). The condition should be considered when large ecchymotic patches involving the limbs are the only findings. Fleabites, especially in low socioeconomic classes, should be considered in cases presenting with minute petechial spots over the trunk.

(b) Acute purpura with bad general condition

In this group, the patient is critically sick often necessitating hospitalization and purpura is not the most prominent feature of illness. Thrombocytopenia is present and other laboratory findings depend on the causative disease. CBC, CRP, study of coagulation mechanism and evaluation of renal function are the most relevant investigations. The main causes are:

1. Disseminated intravascular coagulation (DIC): It is a disease characterized by consumption of platelets and some coagulation factors (1, 2, 5, 8) in a process of formation of minute intravascular clots. It occurs as a complication of another severe systemic illness. The main precipitating factors are septicemia, shock and acidosis. Severe gastroenteritis with dehydration, shock and acidosis is an ideal situation for DIC to develop.

- Clinically, the patient is critically sick and the features of the precipitating disease are well evident (as septicemia, shock, acidosis). The hematological manifestations of the disease include bleeding from puncture sites and surgical incisions, purpura (petechiae and ecchymoses) and necrotic skin patches (characteristic of DIC). Internal hemorrhage (including intracranial hemorrhage) may occur due to thrombocytopenia and severe coagulation defect.

- Laboratory diagnosis depends on the presence of (1) Thrombocytopenia, (2) Severe coagulation defect (prolonged thrombin, prothrombin and partial thromboplastin times) and (3) Fibrin degradation products (FDPs) in the peripheral blood.

- Prognosis is generally bad and it depends on the proper control of the precipitating factors and the extension of internal hemorrhage.

2. Hemolytic uremic syndrome: It is a syndrome of acute hemolytic anemia, acute renal failure, thrombocytopenia and distorted red cells. The disease mostly occurs in children below the age of 4 years and usually following gastroenteritis or upper respiratory tract infection.

- Clinically, the manifestations of acute hemolysis (intense pallor), acute renal failure (oliguria, acidotic breathing and altered consciousness) and thrombocytopenia (purpura) are present. The patient is critically sick, necessitating urgent hospitalization.

- Laboratory diagnosis depends on the presence of acute hemolysis (anemia, reticulocytosis), distorted red cells, thrombocytopenia and acute renal failure. The condition should be differentiated from bilateral renal vein thrombosis and septicemia because in these 3 conditions acute hemolysis, acute renal failure and thrombocytopenia may coexist (see acute hemolytic anemia and acute renal failure).

3. Bilateral renal vein thrombosis: It may follow severe gastroenteritis and dehydration. Gross hematuria, flank masses and acute renal failure are the main features. As acute hemolysis and thrombocytopenia may also occur, differentiation from hemolytic uremic syndrome is important (abdominal ultrasound is essential).

4. Severe septicemia: Severe bacterial agents (especially meningococci) can produce severe septicemia and purpura. The mechanism of purpura is both vascular and thrombocytopenic (direct platelet destruction or consumptive thrombocytopenia).

• Clinically, the patient is critically sick with high fever, toxic look, pallor and may be persistent vomiting and altered consciousness. Complications as septic shock, acute hemolytic anemia, DIC and acute renal failure may also occur (see short febrile illness).

• Laboratory diagnosis of septicemia depends on the presence of polymorphonuclear leukocytosis, bandemia, toxic granulations, elevated CRP and may be positive blood culture. Thrombocytopenia may be also present (consumptive thrombocytopenia).

• Septicemia with a purpuric rash should be differentiated from other causes of acute purpura in critically sick patient and from other infections (mostly viral) with a fever and purpuric rash.

Differential diagnosis of septicemia with purpura

From other causes of acute purpura in critically sick patient
- Disseminated intravascular coagulation.
- Hemolytic uremic syndrome.
- Bilateral renal vein thrombosis.

From other causes of fever and purpuric rash (good general condition)
- Enterovirus infection (especially echovirus type 9).
- Cytomegalovirus infection.
- Hemorrhagic (or black) measles and other rare hemorrhagic fevers (as Dengue lever, Dengue hemorrhagic lever and yellow fever).

• Fever with a purpuric rash is viral in 80% of cases and bacterial in 20% of cases. The general condition and some investigations (CBC, CRP, lumbar puncture) are important in differentiation.

B) CHRONIC PURPURA

In chronic purpura, the onset is usually ***insidious*** and the duration of illness is prolonged over several weeks or months. Associated clinical manifestations as anemia, lymphadenopathy, hepatosplenomegaly, abdominal mass or arthritis are useful to put some possibilities forward.

Diagnostic significance of some clinical signs in chronic purpura

Anemia: Almost all causes of chronic purpura are associated with chronic anemia (except hypoplastic hrombocytopenia and Wiskott-Aldrich syndrome).
Lymphadenopthy: Leukemia, lymphoma.
Splenomsgaly or hepatosplenomegaly: Leukemia, lymphoma, hypersplenism.
Abdominal mass: Lymphoma. neuroblastoma.
Arthritis: Leukemia, lymphom, neurobtastoma.
Skeletal anomalies: Fanconi anemia.
Eczema and recurrent infections (in a male): Wiskott-Aldrich syndrome.

Laboratory investigations including bone marrow examination are essential for diagnosis.

Diagnostic significance of laboratory investigations in chronic purpura

Complete blood count (CBC)

Thrombocytopenia only

Early aplastic anemia, hypoplastic thrombocytopenia or Wiskott-Aldrich syndrome.

Pancytopenia: All causes (except hypoplastic thrombocytopenia, Wiskott-Aldrich syndrome).

Blast cells: Acute leukemia.

Hypersegmented neutrophils (shift to right): Megaloblastic anemias.

Bone marrow examination

Hypoplastic bone marrow (decreased megakaryocytes only)

Hypoplastic thrombocytopenia or early aplastic anemia.

Aplastic bone marrow (decreased precursors of the 3 blood elements)

Aplastic anemia, leukemia, bone marrow replacement.

Abnormal cells: Leukemia, lymphoma, neuroblastoma, Gaucher cells.

Erythroid hyperplasia: hypersplenism, megaloblastic anemias.

Other investigations

Reticulocytosis:Chronic hemolytic anemia, immune thrombocytopenia.

Strongly positive direct Coomb's test: Immune pancytopenia.

Lymph node biopsy: With suspected lymphoma.

Abdominal ultrasound: With abdominal masses (lymphoma, neuroblastoma).

Skeletal survey: With associated anomalies or suspected osteopetrosis.

According to the number of megakaryocytes in the bone marrow, patients with chronic purpura are classified into 2 groups

(a) Chronic purpura with hypoplastic or aplastic bone marrow

In this group, peripheral blood examination reveals ***thrombocytopenia or pancytopenia*** and bone examination reveals decreased number of megakaryocytes with or without aplasia of the bone marrow or infiltration with malignant cells.

1. Aplastic anemia (aplastic pancytopenia): Purpura (thrombocytopenia) usually appears first followed by anemia and leukopenia. There is no lymphadenopathy or hepatosplenomegaly. Peripheral blood examination reveals pancytopenia and bone marrow is hypocellular with decreased precursors of the 3 blood elements (aplastic bone marrow). No abnormal cells in bone marrow examination (see chronic anemias).

2. Hypoplastic thrombocytopenia: Isolated thrombocytopenia without or with anomalies (thrombocytopenia absent radius syndrome) should be considered when bone marrow reveals decreased number of megakaryocytes with normal precursors of erythrocytic and granulocytic series. Differentiation from early aplastic pancytopenia requires repeated evaluation. In aplastic pancytopenia, diminished precursors of granulocytic and erythrocytic series appear on repeated bone marrow examination.

3. Acute leukemia: Purpura is usually associated with anemia. Other clinical manifestations as prolonged fever, lymphadenopathy, hepatosplenomegaly and arthritis are commonly present. Diagnosis depends on the detection of blast cells in the peripheral blood and bone marrow (see common malignancies).

4. Bone marrow replacement: Bone marrow replacement or infiltration may occur with malignant diseases (lymphoma, neuroblastoma) or metabolic conditions (Gaucher disease, osteopetrosis). Bone marrow examination is essential to reveal the characteristic cells.

(b) Chronic purpura with normal or hyperactive bone marrow

In this group, peripheral blood examination reveals ***thrombocytopenia or pancytopenia*** and bone marrow is normal with normal or increased number of megakaryocytes. Erythroid hyperplasia or megaloblastic changes may be also present.

1. Wiskott-Aldrich syndrome: It is an x-linked disease characterized by thrombocytopenia, eczema and increased susceptibility to infection. Patients usually have history of prolonged bleeding following circumcision and bloody diarrhea in infancy. Atopic dermatitis and recurrent infections usually appear in the first year. The disease should be considered in males with chronic thrombocytopenia and normal megakaryocytes in bone marrow. The prognosis is generally bad as survival beyond the second decade is rare. Infections, bleeding and EBV- associated malignancies are the main causes of death.

2. Hypersplenism: Destruction of the 3 blood elements by the hyperactive spleen will lead to pancytopenia. The condition may complicate longstanding cases of chronic hemolytic anemias or metabolic diseases as Gaucher disease. Splenomegaly or hepatosplenomegaly is an important clinical sign.

3. Immune pancytopenia: Immune destruction of the 3 blood elements may accompany cases of lymphoma or systemic lupus erythematosus. Direct Coomb's test is strongly positive.

4. Megaloblastic anemias: Anemia is the main finding and it is macrocytic in type. Leukopenia and thrombocytopenia may also occur. Bone marrow examination reveals megaloblastic changes (see megaloplastic anemias).

3. Coagulation Disorders

Inherited coagulation disorders	Acquired coagulation disorders
Hemophilias Other coagulation defects	Vitamin K deficiency Disseminated intravascular coagulation Severe liver disease

Bleeding disorders include purpuras and coagulation disorders.

- ***Purpuras*** result from a defect in the *primary hemostatic mechanism* (vascular defect, platelet deficiency or platelet dysfunction). The skin lesions are in the form of petechiae and multiple small ecchymotic patches. Bleeding is mainly from the small vessels of the mucous membranes (epistaxis, bleeding gums, hematuria).
- ***Coagulation disorders*** result from a defect in the *secondary hemostatic mechanism* (deficiency of coagulation factors). The skin lesions are in the form of large and extensive ecchymotic patches. Minor blunt trauma could be followed by extensive bruising. Bleeding occurs in 2 forms: (1) Persistent bleeding or oozing following minor trauma as venipuncture, tooth extraction or circumcision and (2) Deep bleeding into muscles (intramuscular hematoma) and joints (hemarthrosis).
- ***Both defects*** may coexist as in vascular hemophilia and DIC.

Laboratory evaluation of the hemostatic mechanism

Primary hemostatic mechanism

Bleeding time (normally, 4 -8 minutes): Prolonged with primary defects.

Platelet count (normally, 150.000 - 250.000):

- 50.000 - 100.000: Mild thrombocytopenia.
- 20.000 - 50.000: Moderate thrombocytopenia (Purpura, bleeding).
- Less than 20.000: Severe thrombocytopenia (serious bleeding may occur).

Platelet function (platelet adhesiveness, platelet aggregation, clot retraction).

Secondary hemostatic mechanism

Thrombin time (normally, 15-20 seconds): Prolonged in factor 1 deficiency.

Prothrombin time (normally, 12-14 seconds): Prolonged in factors 2, 5, 7 or 10 deficiency.

Partial thromboplastin time (normally, 25-40 seconds): Prolonged in phase I defects as factor 8, 9,11 or 12 deficiency.

A) INHERITED COAGULATION DISORDERS

Inherited coagulation disorders are characterized by the following:

1. Early onset of bleeding (usually in infancy or early childhood).

2. Bleeding is repeated, often following minor blunt trauma or venipuncture. Major trauma results in hematomas, hemarthrosis or serious internal hemorrhage.

3. Positive family history is frequently present.

Inherited coagulation disorders include hemophilias and other disorders.

(a) Hemophilias

Hemophilias are a group of inherited disorders that result from a defect in phase I coagulation. There are 4 types that differ in incidence, mode of inheritance and severity of bleeding. The common laboratory abnormality in all types is the *prolonged partial thromboplastin time* (more than 40 seconds).

Types of hemophilia

	Incidence	Deficient factor	Inheritance	Bleeding
Hemophilia A	80%	Factor 8	X-linked recessive	Severe.
Hemophilia B	10%	Factor 9	X-linked recessive	Severe.
Hemophilia C	2%	Factor 11	Autosomal recessive	Mild
Vascular hemophilia	8%	Von Willebrand	Autosomal dominant	Moderate.

- **Factor 12 deficiency** (Contact factor deficiency) is not associated with any clinical manifestations in spite of the prolonged partial thromboplastin time (i.e. nonbleeding disorder).
- **Parahemophilia (Owrens disease)** is not a true hemophilia because the coagulation defect (factor 5 deficiency) is belonging to phase II coagulation. Clinically, it is similar to hemophilia A and B with the difference of being an autosomal recessive disorder. Prolonged prothrombin time is the main laboratory abnormality.

1. Hemophilia A (classic hemophilia): It is the most common type (80% of cases). It is an x-linked disease caused by deficiency of factor 8 (antihemophilic factor). The clinical severity depends on the level of factor 8 activity in plasma. It is 6-30% of normal (in mild cases), 1-5% (in moderate cases) and below 1% (in severe cases).

- The most characteristic features of hemophilia A are spontaneous or traumatic hemorrhages which can be subcutaneous, intramuscular or within joints (hemarthrosis). In infants, excessive bleeding may follow circumcision, but bleeding is usually not evident in the first year of life. After infancy, with the time the child begins to walk, easy bruising and hemarthrosis become evident.
- Laboratory diagnosis depends first on the presence of prolonged partial thromboplastin time (phase I defect). Coagulation abnormalities can be corrected by addition of normal plasma. A specific assay for factor 8 activity confirms the diagnosis (6-30 units/dl in mild cases, 1-5 units/dl in moderate cases and less than 1 unit/dl in severe cases). Bleeding time and platelet adhesiveness are normal (important differentiating points from vascular hemophilia).

2. Hemophilia B (Christmas disease): It is the second most common type of hemophilia (about 10% of cases). It is an x-linked disease caused by factor 9 deficiency. Clinically, it cannot be differentiated from hemophilia A. Partial thromboplastin time is prolonged and the abnormality can be corrected by addition of serum and not by plasma. A specific factor 9 assay is essential for accurate differentiation from hemophilia A.

3. Hemophilia C (factor 11 deficiency): It is the least common type (only 2% of cases). It is an autosomal recessive disease caused by factor 11 deficiency. Bleeding is usually mild (recurrent epistaxis) and occurs only in homozygous patients with factor 11 activity less than 10% of normal. Partial thromboplastin time is prolonged and coagulation abnormalities can be corrected by both plasma and serum. Factor 11 activity is reduced (less than 10 units/dl).

4. Von Willebrand disease (VWD): It is recently considered as the most common hereditary bleeding disorder (1-2% of general population). It is an autosomal dominant disease caused by a *deficiency of Von Willebrand Factor (VWF)*. This factor is a large multimeric glycoprotein that is synthesized in megakaryocytes and endothelial cells. VWF has 2 components or 2 functions (1) high molecular weight multimers, which are responsible for platelet-adhesiveness and (2) factor 8 carrying protein (to carry factor 8 in plasma). As a result of VWF deficiency, platelet adhesiveness and factor 8 activity are reduced.

- The disease has 3 variants or 3 types according to the degree and type of VWF deficiency. ***Type I*** is the most common (85% of cases). VWF is deficient but not absent and factor VIII activity is reduced or normal. ***Type II*** VWD is characterized by reduced factor VIII binding activity of VWF but platelet adhesiveness is normal. This type is also known as *autosomal hemophilia*. It has several subtypes (Type 2A, Type 2B, type 2N and Type 2M). ***Type III*** is the homozygous inheritance of VWF deficiency. It is characterized by absent VWF and very low levels of factor VIII.

Types of Von Willebrand disease

	Type I	Type II	Type III
Von Willebrand Factor	Deficient (Heterozygous)	Reduced binding to factor VIII	Absent (homozygous)
Platelet adhesiveness	Reduced	Normal	Reduced
Factor VIII activity	↓ or Normal	Reduced	1-3% only

- Clinically, bleeding is usually mild to moderate. However, severe hemorrhage may occur following trauma. Hemarthrosis is rare.
- Laboratory diagnosis depends on the presence of (1) prolonged partial thromboplastin time, (2) prolonged bleeding time, (3) reduced VWF, platelet adhesiveness and factor 8 activity according to the type (see above).

(b) Other inherited coagulation disorders

These disorders are generally rare.

1. Phase II disorders: These disorders include factor 2 deficiency (hypoprothrombinemia), factor 2 abnormal function (dysprothrombinemia), factor 5 deficiency (Owren's disease), factor 7 or 10 deficiency. All these disorders are inherited as autosomal recessive diseases. Bleeding and bruising are the main features. Prolonged prothrombin time is the main laboratory finding.

• *Factor 5 deficiency* (Parahemophilia or Owrens disease) is not a true hemophilia as the coagulation defect is belonging to phase II coagulation. Clinically, it is similar to hemophilia A and B with the difference of being an autosomal recessive disorder. Prolonged prothrombin time is the main laboratory abnormality.

2. Phase III disorders: Deficiency of factor 1 (congenital afibrinogenemia) and factor 13 (fibrin-stabilizing factor deficiency or transglutaminase deficiency) are the 2 main diseases.

• *Factor 1 deficiency* (congenital afibrinogenemia) is an autosomal recessive disorder characterized by mild bleeding and rare hemarthroses. Patients may present in neonatal period with gastrointestinal bleeding. Prolonged thrombin time is the main finding and in absence of DIC, unmeasurable fibrinogen level is diagnostic.

• *Factor 13 deficiency* (fibrin-stabilizing factor or transglutaminase deficiency) is characterized by mild bruising; delayed separation of umbilical stump beyond 4 weeks and poor wound healing. The usual screening tests for hemostasis are normal. The screening tests for factor XIII depends on the observation that there is increased solubility of the clot. These patients benefit with cryoprecipitate infusion every 3-4 weeks.

B) ACQUIRED COAGULATION DISORDERS

1. Vitamin K deficiency: Vitamin K is a fat-soluble vitamin required for the prothrombin complex (factors 2, 7, 9, 10). Beyond the early neonatal period (hemorrhagic disease of the newborn), vitamin K deficiency is uncommon. The main causes are deficient intake (vomiting and prolonged fasting), deficient intestinal synthesis (prolonged antibiotic therapy) and deficient absorption (chronic diarrhea).
Coagulation abnormalities include prolonged phase I (partial thromboplastin time) and phase II (prothrombin time). Bleeding usually responds dramatically to parenteral vitamin K administration. Failure of response suggests DIC or severe liver disease.

2. Disseminated intravascular coagulation (DIC): In DIC, the platelets and some coagulation factors (1, 2, 5, 8) are consumed in a process of formation of minute intravascular clots (consumptive coagulopathy). The causes of bleeding are thrombocytopenia and multiple coagulation defects (prolonged thrombin, prothrombin and partial thromboplastin times). It occurs as a complication of another severe systemic illness. The main precipitating factors are septicemia, shock and acidosis. Severe gastroenteritis with dehydration, shock and acidosis is an ideal situation for DIC to develop.

• Clinically, the patient is critically sick and the features of the precipitating disease are well evident (as septicemia, shock, acidosis). The hematological manifestations of the disease include bleeding from puncture sites and surgical incisions, purpura (petechiae and ecchymoses) and necrotic skin patches (characteristic of DIC). Internal hemorrhage (including intracranial hemorrhage) may occur due to thrombocytopenia and severe coagulation defect.

• Laboratory diagnosis depends on the presence of (1) Thrombocytopenia, (2) Severe coagulation defect (prolonged thrombin, prothrombin and partial thromboplastin times) and (3) Fibrin degradation products (FDPs) in the peripheral blood.

3. Severe liver disease: In acute and chronic liver failure, both vitamin K dependent factors (2, 7, 9, 10) and vitamin K independent factors (1, 5) are reduced leading to prolongation of the 3 phases of coagulation (as in DIC). Factor 8 is not reduced in liver disease (important differentiating point from DIC).

• In case of hepatosplenomegaly, other causes of bleeding may coexist as hypersplenism (thrombocytopenia) and portal hypertension (esophageal varices).

Acquired coagulation defects

Vitamin K deficiency: Prolonged phase I and II.
DIC: Prolonged phase I, II and III. Factor 8 is reduced.
Liver disease: Prolonged phase I, II and III. Factor 8 is normal.

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Common Malignancies

1. Leukemias.
2. Lymphoma.
3. Brain Tumors.
4. Neuroblastoma.
5. Wilms Tumor.
6. Rhabdomyosarcoma.
7. Retinoblastoma.

Common Malignancies

Malignancy	Relative incidence	Age of peak incidence
1. Acute leukemia	35% of all cases	3 - 10 years
2. Brain tumors	25% of all cases	5 - 10 years
3. Lymphoma	15% of all cases	At any age
4. Neuroblastoma	8% of all cases	Below 3 years
5. Wilms tumor	5% of all cases	2 - 5 years
6. Rhabdomyosarcoma	4% of all cases	Below 5 years
7. Retinoblastoma	3% of all cases	Below 3 years

All other malignancies account for less than 5% of cases

Malignant neoplasms are not uncommon in pediatric age group. Following infections, trauma and congenital anomalies, malignant neoplasms are a leading cause of death in children.

Although most cases of cancer in pediatric age group occur in children, infants also can be affected especially with neuroblastoma and retinoblastoma.

For early diagnosis and better prognosis, the clinical presentations of common malignancies should be always in mind. Picture of bone marrow failure (chronic anemia, chronic purpura), lymphadenopathy, increased intracranial pressure and abdominal mass are by far the most common clinical presentations.

For each neoplasm, the following 5 questions are clinically important:

1. What is the peak age of incidence?
2. What are the main clinical presentations?
3. How to confirm the diagnosis?
4. What is the type?
5. What is the prognosis?

1. Leukemias

Acute lymphoblastic leukemis (77%)	**Acute myelogenous leukemia** (11%)	
Early pre B type (50% of all cases)	Myeloblastic, on maturation	(M1)
Pre B type (16%)	Myeloblastic, some maturation	(M2)
T type (10%)	Promyelocytic	(M3)
B type (less than 1%)	Myelomonocytic	(M4)
	Monocytic	(M5)
	Erythroleukemia	(M6)
	Megalokariocytic	(M7)

Chronic myelogenous leukemia (5%) has 2 forms (adult and juvenile forms)
Unclassified acute and chronic forms (7% of cases)

Leukemia is a generalized neoplastic proliferation, rapid or slow, of one of the leukocytopoietic tissue, often associated with abnormal white cell count. It is the most common form of childhood cancer as it accounts alone of about 35% of all cancers.

The cause is not exactly known but both genetic factors (as Down syndrome, Fanconi syndrome, Turner syndrome, ataxia telangiectasia) and environmental factors (radiation, drugs, alkylating agents, benzene exposure) could be responsible.

1. *What is the peak age of incidence?*

- In acute lymphoblastic leukemia, the peak age of incidence is between 3 - 5 years.
- In acute myelogenous leukemia, the incidence is higher in late childhood.
- Chronic myelogenous leukemia has 2 forms. The juvenile form occurs below the age of 2 years while the adult form is mostly above the age of 10 years.

2. *What are the main clinical presentations?*

Patients with **acute leukemia** usually come to medical consultation within 1-2 months of onset. They usually present with one or more of the following 5 presentations (in order of frequency).

a) Anemia: It is present in almost all cases due to the progressive bone marrow replacement by the malignant cells.

b) Purpura: Petechial rash and ecchymotic patches are present in about 70% of cases at the time of diagnosis.

c) Hepatosplenomegaly and genendized lymphadenopathy: They are present in more than 50% of cases.

d) Arthritis and bone pains: Arthritis is the main presentation is about 30% of cases.

e) Prolonged fever: It is usually present in about 25% of cases.

• Clinical differentiation between acute lymphoblastic and acute myelogenous leukemia cannot be made on clinical grounds. However, rapid progression of symptoms, gingival swelling and active bleeding should suggest acute myelogenous leukemia. On the other hand, mediastinal compression (dyspnea and prominent neck veins) suggests T type of acute lymphoblastic leukemia.

In **chronic myelogenous leukemia,** clinical presentations depend on the type. In the *juvenile form*, rashes, lympadenopathy and splenomegaly are usually present. In the *adult form*, splenomegaly without any evident hematological findings is the main presentation. Huge splenomegaly in a child above the age of 10 years should always raise the possibility of adult form of chronic myelogenous leukemia.

3. How to confirm the diagnosis?

In patients with **acute leukemia,** the main investigations are:

a) Peripheral blood examination: Demonstration of blast cells (above 2%) is the most important laboratory finding (however, absence of blast cells does not exclude the diagnosis). Anemia and thrombocytopenia are commonly present and the white cell count is normal, low or high.

b) Bone marrow examination: It is the most definitive diagnostic procedure. In acute lymphoblastic leukemia, more than 25% of all marrow cells are lymphoblasts. However, in most cases, it is completely replaced by leukemic blast cells. In acute myelogenous leukemia, the bone marrow is hypercellular and the predominant cell type can be identified according to French American British (FAB) classification (7 types from M1 to M7).

c) CSF examination: It is important to detect CNS involvement. Presence of leukemic blast cells in CSF indicates meningeal affection.

d) Radiological studies: Chest x-ray is important for detection of mediastinal involvement, which is common in T type of acute lymphocytic leukemia. Skeletal survey is also important for cortical defects and subperiosteal bone resorption.

Acute leukemia should be differentiated from other causes of *bone marrow failure* especially aplastic anemia, lymphoma and neuroblastoma (see chronic purpura).

Differential diagnosis of acute leukemia

Other causes of bone marrow failure: Aplastic anemia, lymphoma, neuroblastoma
Other causes of arthritis.
Other causes of prolonged fever.

In patients with suspected **chronic myelogenous leukemia,** peripheral blood examination reveals ***marked leukocytosis*** (usually above 100.000 in the adult form). The Philadelphia chromosome is present in adult form while in the juvenile form, fetal hemoglobin is elevated (30 -70%).

4. *What is the type?*

In **acute leukemia,** laboratory differentiation between acute lymphoblastic and acute myelogenous leukemia depends on the cytochemical characteristics of the blast cells.

Cytochemical characteristics of blast cells in acute leukemia

Acute lymphocytic leukemia	Acute myleogenous leukemia
Absent Sudan black "B" granules Absent peroxidase granules Clumped reaction of PAS	Positive Sudan black "B" granules Positive peroxidase granules Diffuse reaction of PAS

PAS: Periodic acid-Schiff stain.

- ***Acute lymphoblastic leukemia*** is subdivided into 4 types according to the presence of cell membrane markers (early pre B, pre B, T type and B type). Early pre B is the most common and the one with the best prognosis.
- ***Acute myelogenous leukemia*** is subdivided into 7 types (from M1 to M7) according to the French-American British (FAB) classification. Monoclonal antibodies are also useful in classification,

In **chronic myelocytic leukemia,** the subclassification into juvenile and adult forms depends on the age and the presence or absence of Philadelphia chromosome and fetal hemoglobin (see above).

5. *What is the prognosis?*

In **acute leukemia,** prognosis depends on the type and the subtype.

- ***Acute lymphoblastic leukemia*** has a better prognosis than acute myelogenous. Early pre B type has the best prognosis (95% of cases go into remission with therapy), followed by pre B and T types. B type has the worst prognosis.
- ***Acute myelogenous leukemia*** has a less favorable prognosis. Only 65% of cases go into remission with therapy. Relapses occur in 90% of cases.

In **chronic myelogenous leukemia,** the prognosis is generally bad. Most cases die within 3 years of onset.

2. Lymphomas

Hodgkin disease (30%)	**Non-Hodgkin lymphoma (NHL)** (70%)
Nodular sclerosis (50%) Mixed cellularity (30%) Lymphocyte predominance (15%) Lymphocyte depletion (5%)	Lymphoblastic NHL Small noncleaved cell lymphoma (SNCCL) Large cell lymphoma (LCL) (Diffuse and anaplastic subtypes)

Burkitt's lymphoma is typically a jaw tumour of African children.

Lymphomas are the third most common neoplasm in children (about 15% of all cases). Above the age of 10 years, lymphomas are the commonest neoplasm. Non-Hodgkin lymphoma (NHL) is commoner and more serious than Hodgkin disease.

Hodgkin disease is almost always a nodal disease (arises from the lymph nodes in 99% of cases). **Non-Hodgkin lymphoma** has 3 sites of origin: (1) Extranodal lymphatic tissue as lungs and GIT (most common), (2) Nodal disease (next common) and (3) extralymphatic tissue as skin, bones, breast, orbit or parotids (least common). This explains why non-Hodgkin lymphoma has a wide range of presentations.

1. What is the age of peak incidence?

Hodgkin disease is rare below the age of 5 years. The peak incidence is between 15 - 35 years and above 50 years.

Non-Hodgkin lymphoma occurs at any age. Generally, most cases of lymphoma below the age of 10 years are of the non-Hodgkin type.

2. What are the main clinical presentations?

Lymphomas usually present with one or more of the following presentations (some presentations as abdominal mass and primary bone disease are peculiar to NHL).

1. Lymphadenopathy: It is the commonest presentation. Cervical lymph nodes are the commonest primary site. Occasionally, supraclavicular, axillary or inguinal nodes are the primary sites. The nodes are significantly or hugely enlarged, firm, discrete, nontender with no regional inflammation to explain it. Single or multiple groups can be involved. The enlargement is usually discovered by the patient or his parents. ***Splenomegaly*** may be also found.

2. Mediastinal mass: Mediastinal lymph node enlargement can be the presentation of Hodgkin or non-Hodgkin lymphoma (especially *lymphoblastic NHL*). It presents clinically with progressive dyspnea and features of superior vena caval obstruction (dilated veins over the upper part of the anterior chest wall with neck or facial edema). Chest x-ray clearly demonstrates the mediastinal widening.

3. Abdominal mass: Big intraabdominal or retroperitoneal mass can be the main presentation of non-Hodgkin lymphoma especially *small noncleaved cell lymphoma* (more than 80% of cases of SNCCL present with abdominal mass). Ascites can be also present (see abdominal masses).

4. Primary bone disease: It can be the initial presentation of non-Hodgkin lymphoma especially *large cell lymphoma (LCL)*. Progressive spinal cord compression (paraplegia) should always raise suspicion.

5. Malignant malaise: Prolonged fever, anorexia, malaise, night sweating and weight loss can be the presentation of both Hodgkin or non-Hodgkin lymphoma.

6. Pancytopenia: It is usually a manifestation of an advanced disease. It occurs due to either bone marrow infiltration or immune destruction of the 3 blood elements. Anemia, purpura and increased susceptibility to infection are clinically evident (see chronic purpura).

3.How to confirm the diagnosis?

1. Nodal biopsy: It is the most reliable method for diagnosis and identification of the pathological type especially in cases presenting with lymphadenopathy. More than one nodal biopsy may be needed.

2. Bone marrow biopsy: It may reveal the characteristic cells when the bone marrow is involved.

3. Radiological studies: Chest x-ray (mediastinal mass) and skeletal survey (bone involvement) are important for assessment of the spread of the disease. CT scan of the chest, abdomen and spine are also important.

4. What is the type?

With nodal biopsy (and other biopsies), the histological type can be identified as Hodgkin disease or non-Hodgkin lymphoma.

In **Hodgkin disease,** the characteristic malignant cell is the "Reed-Sturnberg cell". It is a large cell with multiple or multilobulated nuclei. The disease is histologically divided into 4 subtypes with different incidence and prognosis. Nodular sclerosis is the most common type (50% of cases), followed by mixed cellularity (30%), lymphocyte predominance (15%), lymphocyte depletion (5%).

In **non-Hodgkin lymphoma,** malignant cells can be classified in different ways:

- ***According to grade of malignancy:*** Low grade and high grade. Most childhood lymphomas are of the high-grade type.
- ***Histologically***, it can be classified as lymphoblastic NHL, small noncleaved cell lymphoma (SNCCL) and large cell lymphoma (LCL).
- ***Immunologically,*** It can be classified as T-cell type (as in lymphoblastic NHL) or B cell type (as in SNCCL) or either T or B (as in LCL)

5. *What is the prognosis?*

Prognosis depends on the type, subtype and the stage:

• ***Type:*** Hodgkin disease has a much better prognosis than non-Hodgkin lymphoma. With Hodgkin disease, more than 90% of cases go into long remission with therapy, while in non-Hodgkin lymphoma only 50% of cases can achieve that long remission.

• ***Subtype:*** In Hodgkin disease, lymphocyte predominance has the best prognosis followed by nodular sclerosis, mixed cellularity and lymphocyte depletion. In non-Hodgkin lymphoma, T-cell type has a better prognosis than the B-cell type.

• ***Stage:*** Proper staging requires careful clinical and laboratory investigations and sometimes laparotomy. There are 4 stages (I to IV) according to the spread of the disease. Stage I has the best prognosis and stage IV has the worst.

Staging system of Hodgkin disease and non-Hodgkin lymphoma

Stage	Hodgkin disease	Non-Hodgkin lymphoma
Stage I	Single lymph node region or Single extralymphatic tissue	Single tumor (nodal or extranodal) (with exclusion of mediastinum or abdomen)
Stage II	2 or more lymph node regions on same side of diaphragm	2 or more tumors (same side of diaphragm) or Primary gastrointestinal tumor
Stage III	2 or more lymph node regions on both sides of diaphragm	2 or more tumors (both side of diaphragm) or Primary intrathoracic tumor
Stage IV	Diffuse disseminated disease	Involvement of CNS or bone marrow

Contrasting Hodgkin disease and non-Hodgkin lymphoma

Features	Hodgkin disease	Non-Hodgkin lymphoma
Entity	Single disease	Multiple diseases
Incidence	Less common	More common
Origin	Almost always nodal	Extranodal is commoner
Clinical presentations	Few	Several
Prognosis	More favorable	Less favorable

3. Brain Tumors

Posterior fossa (40%)	Hemispheric (37%)	Midline (14%)
Cerebellar astrocytoma (15%) Medulloblastoma (15%) Brainstem glioma (15%) 4th V. ependymoma (4%)	Low grade astrocytoma (23%) High grade astrocytoma (11%) Other gliomas (3%)	Craniopharyngioma (8%) Chiasmal glioma (4%) Pineal region tumours (2%)

Choriod plexus papilloma arises from the ependymal lining of the ventricular wall (lateral ventricles, third ventricle or fourth ventricle). It is the commonest tumor in infancy.

Next to leukemia, brain tumors are the most common malignancy in childhood (about 25% of all malignancies). Tumors arising from the posterior fossa account for 40% of cases followed by hemispheric tumors (37%) and midline tumors (14%).

1. What is the peak age of incidence?

Although brain tumors can occur at any age including infancy, most cases occur during the second half of the first decade (5 - 10 years). Patients with neurocutaneous syndromes (as neurofibromatosis) are at increased risk of brain tumors, which may occur even in infancy.

2. What are the main clinical presentations?

Brain tumors can present in different ways according to the location, type and rate of growth. Posterior fossa tumors usually present with increased intracranial pressure and/or ataxia while hemispheric and midline tumors usually present with focal neurological signs or endocrinal manifestations.

1. Increased intracranial pressure: Progressive increase in intracranial pressure is the most common presentation of posterior fossa tumors. It occurs due to obstructive hydrocephalus which results from obstruction of CSF flow in the fourth ventricle or acqueduct of Sylvius. Choroid plexus papilloma results in increased CSF production and communicating hydrocephalus. Signs of increased intracranial pressure may develop rapidly within few weeks (as in medulloblastoma) or may progress slowly over several weeks or months (as in cerebellar astrocytoma).

- Clinical manifestations of increased intracranial pressure vary with age:

a) In infancy, progressive increase in head size with separation of sutures and bulging fontanel is the main presentation, so brain tumors should be always included in the differential diagnosis of macrocephaly (see large head).

b) In childhood, morning headache, morning vomiting and diplopia are the main symptoms. *Headache* is usually dull and generalized and it is improved with standing up or vomiting and worsened by coughing or straining during defecation. *Vomiting* is

usually not preceded by nausea and it often relieves the headache. *Diplopia* may result in head tilting in a trial to compensate for the blurred image (fundus examination is essential for demonstration of papilloedema).

- The main complications of markedly increased intracranial pressure are *deterioration of visual acuity* and development of *herniation syndromes*. Herniation can be central transtentorial, uncal or by cerebellar tonsils through foramen magnum (see coma).

Differential diagnosis of chronic increased intracranial pressure

Acute increased intracranial pressure

The mechanism of increased ICP is brain edema and not obstruction to CSF flow.
Consciousness is altered and the patient is usually comatose.
Other neurological signs as sluggish pupillary reaction to light, increased muscle tone and tendon reflexes are present (see comatose child).

Other causes of recurrent headache

Vascular headache: Migraine (common cause, bilateral or unilateral).
Muscle contraction headache: Tension headache, psychogenic headache.
Hypertensive headache.
Symptomatic headache: Chronic sinusitis, errors of refraction.

2. Cerebellar ataxia: It is the second most common presentation of posterior fossa tumors. The main manifestations are nystagmus, intention tremors and ataxic gait. Ataxia can be unilateral (as in unilateral cerebellar astrocytoma) or bilateral (as in midline astrocytoma or medulloblastoma). Brain tumors should be always excluded in any child presenting with ataxia.

3. Recurrent convulsions: Focal convulsions with unilateral headache can be the presentation of cerebral hemispheric tumors as cerebral astrocytoma. Spastic hemiparesis may be also present.

4. Progressive motor weakness: Motor weakness with pyramidal tract lesion (hyperreflexia and positive Babiniski sign) may be the presentation. Bilateral multiple cranial nerve palsies (squint, facial palsy, bulbar palsy) with pyramidal tract lesions are the presentation of brainstem glioma.

5. Endocrinal presentations: *Short stature* or *diabetes insipidus* is sometimes the presentations of craniopharyngioma due to pituitary-hypothalamic involvement (Plain skull x-ray shows suprasellar calcification in 90% of cases). *Precocious puberty* especially in males should be taken with concern and brain tumors should be excluded. Optic glioma involving the hypothalamus may present with the picture of *diencephalic syndrome* (severe anorexia, severe wasting and emaciation but with normal linear growth). *Obesity*, on the other hand, can be also the presentation.

3. How to confirm the diagnosis?

With clinical suspicion, computed tomography (CT scan) of the head is the most reliable method for detection and localization of brain tumors. Magnetic resonance imaging (MRI), if available, is more sensitive than CT scan (see Basic Pediatric Radiology and CT Scan in Pediatrics).

Increased intracranial pressure without a demonstrable mass lesion or ventricular dilatation suggests the diagnosis of ***"pseudotumor cerebri"***. With continued features of increased ICP, a second CT scan or MRI are indicated and they may demonstrate an early brain tumor.

Causes of pseudotumor cerebri

Drugs: Prolonged corticosteroid therapy, tetracycline therapy, vitamin A toxicity.
Blood diseases: Iron deficiency anemia, hemolytic anemias, polycythemia.
Endocrinal diseases: Obesity, hypoparathyroidism, pseudohypoparathyroidism.
Intracranial venous obstruction of lateral sinus or posterior sagittal sinus.

4. What is the type?

With CT scan or MRI, brain tumors can be localized and recognized:

1. Posterior fossa tumors: They are the most common group (about 40% of cases). Increased intracranial pressure and/or cerebellar ataxia are the main presentations.

a) Cerebellar astrocytoma: It is a slowly growing tumor, which can be cystic or solid and unilateral or midline. It is the one with the best prognosis

b) Medulloblastoma: It is as common as astrocytoma (15% of cases). It is a rapidly growing tumor, which fills the fourth ventricle and invades the cerebellar hemispheres. Manifestations of increased intracranial pressure develop rapidly over few weeks (see Basic Pediatric Radiology).

c) Brainstem glioma: It may arise from midbrain, pons or medulla. Multiple cranial nerve palsies with pyramidal tract lesions are the main presentation.

d) Fourth ventricle ependymoma: It is the least common. Manifestations of increased intracranial pressure (without ataxia) are the main presentation.

2. Hemispheric tumors: They account for about 35% of cases. Focal neurological signs and increased intracranial pressure are the main presentations:

a) Cerebral astrocytoma: It is the most common brain tumor (34% of all tumors), which can be low-grade (23%) or high-grade (11%). Focal neurological signs as recurrent focal convulsions and /or spastic hemiparesis are the main presentations.

b) Other gliomas: They account only for 3% of cases.

3. Midline tumors: They account for about 14% of cases. Craniopharyngioma is the most common (8%). Clinical presentations vary with type.

a) Craniopharyngioma: It is a tumor arising in the suprasellar region and invading near structures. Clinical presentations include increased intracranial pressure, visual field defects or endocrinal manifestations (short stature or diabetes insipidus). Skull x-ray reveals suprasellar calcification in about 90% of cases. CT scan or MRI clearly demonstrates the tumor in the suprasellar region (see Basic Pediatric Radiology).

b) Chiasmal glioma (optic nerve glioma) is more common in patients with neurofibromatosis. Decreased visual acuity and endocrinal manifestations (diencephalic syndrome or obesity) are the main presentations.

c) Pineal tumors are the least common and they usually present with increased intracranial pressure. It can be clearly demonstrated by CS scan.

The accurate **histological diagnosis** of the tumor (as astrocytoma, medulloblastoma, glioma, ependymoma or oligodendroglioma) cannot be made except after surgical excision and histological study.

5. What is the prognosis?

The general mortality rate of brain tumors is above 50%. However, prognosis depends on the site, type and extension.

- In cerebellar astrocytoma (slowly growing tumor), the prognosis is very good as 90% cure rate can be achieved.
- In cerebral astrocytoma, prognosis depends on the type (low-grade or high-grade).
- In brainstem glioma, the prognosis is very bad as most patients die within 1 year of onset.
- In medulloblastoma (rapidly growing tumor), prognosis also is bad.
- In other tumors, prognosis depends on the site, type and extension.

4. Neuroblastoma

Neuroblstoma is a *unique tumor* with several peculiar characteristics:

1. It is a highly malignant, early metastasizing tumor (about 70% of cases are diagnosed at stage IV).
2. It has a high spontaneous regression rate. Neuroblastoma below the age of 1 year may regress spontaneously without any therapy.
3. It may occur very early even during fetal life.
4. It has multiple diverse clinical presentations.
5. Prognosis depends mainly on the age and not the stage.

Neuroblastoma is the fourth most common malignancy in young children as it accounts for about 8 % of all childhood neoplasms. The tumor may arise from any site containing neural crest cells (adrenal medulla and sympathetic chain).

Sites of origin of neuroblastoma

Adrenal medulla: In 35% of cases.
Sympathetic chain in the abdomen: In 35% of cases.
Sympathetic chain in the chest: In 25% of cases.
Sympathetic chain in the neck or posterior fossa: In 5% of cases.

Neuroblastoma is by far the most common tumor of the neural crest cells. Other tumors are less malignant or benign.

Tumors of the neural crest cells

Tumor	Cells of origin	Nature
Neuroblastoma	Neuroblasts + Sympathogonia	Highly malignant
Ganglioneuroblastoma	Neuroblasts + Ganglion cells	Less malignant
Ganglioneuroma	Ganglion cells	Benign tumor
Pheochromocytoma	Chromaffin cells	Benign or malignant

- **Pheochromocytoma** is a rare tumor which can be benign or malignant, single or multiple and familial or sporadic. Chronic or recurrent episodes of hypertension is the main presentation. Serum and urinarv catecholamines are markedly increased in almost all cases.

1. What is the peak age of incidence?

Most cases of neuroblastoma occur below the age of 3 years. It is the commonest tumor in infancy and it may occur in neonatal period or even during fetal life. Occasionally, neuroblastoma occurs in older children or even adults.

2. What are the main clinical presentations?

Neuroblastoma has several diverse presentations because of the different sites of origin and the early metastasizing nature. Patients may present with one or more of the following 10 presentations

1. Abdominal mass: It is the commonest presentation. The mass is usually discovered accidentally by the parents or during routine abdominal examination. It is a hard, irregular and nontender mass located in the right or left upper quadrant. It enlarges horizontally and commonly crosses the middle line (stage III). The origin is usually the adrenal medulla or the abdominal sympathetic chain.

2. Posterior mediastinal mass: It is the main presentation of tumors arising from the thoracic sympathetic chain. It may be discovered accidentally by chest x-ray or it may present with progressive dyspnea and features of superior vena caval obstruction (dilated veins over the upper part of the anterior chest wall with neck or facial edema). The condition should be differentiated from other causes of mediastinal masses (see Basic Pediatric Radiology and CT scan in Pediatrics).

3. Huge hepatomegaly in infancy: As neuroblastoma is an early metastasizing tumour to the liver, huge hepatomegaly may be the main presentation. The primary tumor can be very small and not detected clinically.

4. Multiple skin nodules in infancy: These nodules are usually firm and purple in color. They mainly occur in infants under the age of 6 months. The prognosis is good and spontaneous regression usually occurs. When the primary tumor is small and remote involvement is limited to the liver, skin or bone marrow, the prognosis is good and the stage is known as stage IV S.

5. Proptosis: Unilateral or bilateral proptosis (due to periorbital metastasis) can be the presentation. A characteristic ecchymotic discoloration of the upper and lower eyelids and surrounding tissues may appear (raccoon-like appearance).

6. Spinal cord compression: Gradual spastic motor weakness with loss of bladder control may be the presentation of the tumor arising from the sympathetic chain.

7. Pancytopenia: Anemia, purpura and increased susceptibility to infections can be the presentation due to widespread bone marrow metastasis.

8. Arthritis and bone pains: They can be the presenting manifestations due to bone metastasis.

9. Chronic diarrhea: Persistent diarrhea to a degree suggesting malabsorption may be the presentation. It occurs due to the effect of the tumor metabolites on alimentary musculature.

10. Episodes of increased adrenergic activity: Episodes of tachycardia, flushing and sweating can be the presentation.

3. *How to confirm the diagnosis?*

1. Urinary catecholamines: It is a good screening test. Both vanillyl mandelic acid (VMA) and homovanillic acid (HVA) are increased in more than 90% of cases.

2. Biopsies: *Bone marrow biopsy* reveals neuroblastoma cells in more than 70% of cases. *Biopsy of skin nodules* (if present) or *liver biopsy* (with hepatomegaly) are also useful.

3. Identification of origin and staging: Several investigations are usually necessary for identification of origin and assessment of the spread of the disease. These investigations include:

- Abdominal ultrasonography.
- CT scan of the abdomen and chest.
- Complete skeletal survey and may be radionuclide skeletal scan.
- Myelography and CT scan of the spine.

4. Postoperative histological examination: It is the definitive way of diagnosis when bone marrow or liver biopsies are negative.

Neuroblastoma staging system

Stage I:	Tumor confined to organ or structure of origin.
Stage II:	Tumor extending beyond organ or structure of origin but not crossing the midline.
Stage III:	Tumor crossing the midline.
Stage IV:	Remote disease involving skeleton, soft tissues, organs or distant nodes.
Stage IV S:	Stage I or II but with remote disease confined only to one or more of the following sites (liver, skin or bone marrow but not bone).

4. *What is the type?*

Histological examination is essential to differentiate neuroblastoma from other tumors of neural crest especially ganglioneuroblastoma and ganglioneuroma (see above).

5. *What is the prognosis?*

Prognosis depends mainly on the age and not the stage:

- Infants below the age of one year have an excellent prognosis due to the high rate of spontaneous regression. Infants presenting with hepatomegaly or skin nodules (stage IV S) have an excellent prognosis.

- In children above the age of 2 years, prognosis depends on the stage. In stages I, II and III, cure rate is about 40%. In stage IV, (70% of cases), cure rate is only 2%.

5. Wilms Tumor (Nephroblastoma)

Sporadic form (98%)	Familial form (2%)
Usually unilateral	Usually bilateral
Lower incidence of congenital anomalies	Higher incidence of congenital anomalies

Wilms tumor (or nephroblastoma) accounts for almost all renal neoplasms in children and for about 5% of all pediatric neoplasms. It can be sporadic or familial and bilateral or unilateral. Sporadic tumor accounts for majority of cases. Familiar form is associated with higher incidence of bilateral disease and associated anomalies (as genitourinary anomalies, hemihypertropny and aniridia). A deletion in chromosome 11 may be also present in the familial form.

1. What is the peak age of incidence?

Wilms tumor commonly presents around the age of 3 years (between 2-5 years).

2. What are the main clinical presentations?

Abdominal mass in upper right or left quadrant (or both) is the main clinical presentation. The mass is asymptomatic and usually discovered accidentally by the parents or during routine abdominal examination. The mass is firm, smooth and does not cross the middle line. (in neuroblastoma, the mass is hard and irregular and commonly crosses the middle line).

Other manifestations as **hypertension** or **hematuria** may be present but are not usually the main presentations.

3. How to confirm the diagnosis?

Abdominal ultrasonography or CT scan of the abdomen is a reliable method for diagnosis of the renal origin. CT scan of the chest is also important for detection of lung metastasis.

4. What is the type?

After surgical excision, histological study will differentiate between Wilms tumor and other rare renal neplasms as mesoblastic nephroma and renal cell carcinoma.

5. What is the prognosis?

It depends on the stage but it is generally good. In stages I, II and III, a relapse free survival can be achieved in 80 - 90% of cases. In stage IV (15% of cases only), relapse free survival is achieved in less than 70% of cases (in neuroblastoma, 70% of cases are diagnosed at stage IV).

6. Rhabdomyosarcoma

Histologic types	Sites of origin
Embryonic type (60%)	Head and neck (40%)
Batryoid type (6%)	Genitourinary (20%)
Alveolar type (15%)	Extremities (20%)
Pleomorphic type	Trunk (10%)
	Retroperitoneal and other sites

Rhabdomyosarcoma is the most common soft tissue sarcomas in children (almost half of the cases) and it accounts for 5% of all childhood cancer. The incidence is higher in white children compared to black children.

1. What is the peak age of incidence?

Most cases occur below the age of 5 years. Extremity lesions occur in older children.

2. What are the main clinical presentations?

The most common presentation is a **mass** that may be painful or painless. Clinical symptoms and signs depend on the site of origin:

a) Nasopharynx: Nasal congestion, mouth breathing, epistaxis, difficulty of swallowing and chewing. Regional extension leads to cranial nerve palsies, blindness and increased intracranial pressure.

b) Face, cheek or neck: Swelling, pain, trismus and may be cranial nerve palsies.

c) Eye: Proptosis, periorbital edema, ptosis, change in visual activity and pain.

d) Middle ear: Pain, hearing loss and chronic ear discharge.

e) Larynx: Croupy cough and progressive stridor

f) Genitourinary: Hematuria, recurrent infections and abdominal or pelvic mass.

g) Extremities: Tumor mass that increases in size.

3. How to confirm the diagnosis?

Biopsy and microscopic examination are necessary for diagnosis. Several months usually elapse between the initial symptoms and biopsy.

4. What is the type?

After surgical excision, histological study will differentiate between the 4 types.

5. What is the prognosis?

In patients with resectable tumor, 80-90% have long disease-free survival. The long term survival of unresectable tumor is around 70%.

7. Retinoblastoma

Unilateral (75%)	Bilateral (25%)
Nonhereditary (60%) Hereditary (15%)	Always hereditary

Retinoblastoma is a common tumor (3% of all childhood malignancies). There is no race or sex predilection. The hereditary form is associated with a germ line defect in the retinoblastoma gene located on chromosome 13.

1. What is the peak age of incidence?

Most cases occur below the age of 3 years. Bilateral involvement occurs in 42% of cases presenting younger than 1 year of age.

2. What are the main clinical presentations?

The most common classic presentation is **leukocoria** (or white papillary reflex). This abnormality is first noticed when the red reflex in not noted in routine ophthamological examination or when the "red eye" is not present in flash photograph of the child. **Strabismus** is commonly the initial presenting complaint. **Orbital inflammation** and **pupil irregularity** occur in advanced cases. **Pain** occurs if secondary glaucoma occurs.

3. How to confirm the diagnosis?

The diagnosis does not require biopsy but **ophthalmologic examination** is usually sufficient to show the characteristic findings. Examination under general anesthesia is usually required to allow complete visualization of both eyes and also photographing of the tumor.

Orbital ultrasonography and CT scan are used to evaluate the extent of intraocular disease and extraocular spread.

4. What is the type?

The histology of retinobastoma is a small round blue cell tumor with rosette formation.

5. What is the prognosis?

More than 90% of cases are cured with chemotherapy and local therapy.

12

Endocrinology

1. Diabetes Mellitus.
2. Hypothyroidism.
3. Adrenocortical disorders.
4. Intersex.
5. Precocious Puberty.

1. Diabetes Mellitus

Type I diabetes mellitus	Type II diabetes mellitus
Other names are: • Insulin-dependent diabetes (IDDM) • Juvenile-onset diabetes	Other names are: • Non-insulin-dependent diabetes (IDDM) • Adult-onset diabetes

Secondary diabetes mellitus (with genetic diseases)

- Chromosomal: Trisomy 21, klinefelter syndrome, Turner syndrome.
- Metabolic: Cystic fibrosis, glycogenosis type I, Hyperlipoproteinemia.
- CNS diseases: Ataxia telangiectasia, Friedreich's ataxia.
- With obesity: Laurence-Moon-Biedle syndrome, Pradder-Willi syndrome.

Diabetes mellitus is the commonest endocrine-metabolic disease in childhood. The general incidence is around 0.2% (2/1000). Most cases of diabetes in children are *"type I diabetes"* or *"insulin-dependent diabetes"*. It is an autoimmune disease characterized by autoimmune destruction of pancreatic islets leading to beta cell failure and decreased or absent insulin secretion. Type II diabetes and secondary diabetes are rare in children.

Causes, pathophysiology and phases of type I diabetes

Causes of autoimmune destruction of beta cells

Genetic predisposition: Inheritance of certain histocompatibility antigens (especially HLA-B8 and HLA-BW 15)

Environmental triggering factors: Viral infections as mumps, varicella, others.

Pathophysiological changes

Hyperglycemia: Leads to glucosuria, osmotic diuresis(polyuria), polydipsia

Proteolysis: Leads to polyphagia, abdominal pain, vomiting and weight loss.

Lipolysis: Leads to ketonemia (ketoacidosis) and ketonuria.

Dehydration results from polyuria and vomiting.

Coma results from dehydration, acidosis and hyperosmolarity.

Phases of diabetes

1. Initial metabolic derangement: High insulin requirements.
2. Initial stabilization: Slight decrease in insulin requirements.
3. Remission or honeymoon phase: Marked decrease in insulin requirements.
4. Intensification: Gradual increase of insulin requirements.
5. Permanent diabetes: Stable insulin requirements

• **Remission or honeymoon phase** occurs in 90% of cases within 1-3 months of initial diagnosis and remains for several weeks or months. During this phase, insulin requirements decrease to less than 50% of initial requirements.

1. *What are the clinical presentations?*

1. Polyuria and polydipsia: Most children with diabetes present clinically with a history of polyuria, polydipsia and weight loss. The duration of symptoms is usually less than one month in most cases. Presence of glucosuria and hyperglycemia (random blood sugar above 160 mg/dl) establish the diagnosis, but in their absence, other causes of polyuria and polydipsia should be considered (see polyuria).

2. Secondary nocturnal enuresis: Bed wetting in a previously trained child should always direct the attention to the possibility of polyuria. Presence of glucosuria and hyperglycemia establish the diagnosis. Other causes of secondary enuresis as urinary tract infection and psychological stresses should be also considered.

3. Diabetic ketoacidosis: Approximately 30% of newly diabetic children will present with diabetic ketoacidocis and 10% of patients with diabetic ketoacidosis are admitted in a comatose state. Diabetic ketoacidosis is a medical emergency, which carries a mortality rate of about 10%.

Diagnostic criteria of diabetic ketoacidosis

Clinical manifestations

Early manifestations: Vomiting, polyuria, ± abdominal pain ± fever.
Next manifestations: Dehydration and acidotic breathing (deep rapid respiration).
Late manifestations: Shock and coma.

Laboratory diagnosis

Hyperglycemia (blood sugar level above 300 mg/dl)
Ketonemia (positive ketone reaction at 1: 2 dilution or greater).
Metabolic acidosis (pH below 7.3 and bicarbonate below 15 mEq/liter).
Glucosuria and ketonuria.

- Vomiting and abdominal pain may be severe to a degree suggesting surgical emergency (as appendicitis or intestinal obstruction)
- Fever can be present due to dehydration or the infection that precipitates the condition. Fever and vomiting can lead to the wrong diagnosis of septicemia.
- The clinical triad of dehydration, acidotic breathing and coma should always raise the possibility of diabetic ketoacidosis.
- Precipitating factors of diabetic ketoacidosis include trauma, infections, vomiting and psychological disturbance.
- Repeated episodes of ketoacidosis in a diabetic child indicates an error in recommended insulin dosage.
- Diabetic ketoacidotic coma should be differentiated from other causes of coma in the diabetic child (see below).

2. *What are the complications?*

Complications of diabetes can be acute or chronic. Acute complications are life threatening and need urgent management. Chronic complications only appear in longstanding cases and do not represent an immediate threat to life.

Complications of type I diabetes

Acute complications

Coma (hyperglycemic or hypoglycemic).
Cerebral oedema (iatrogenic, with hyperosmolar nonketotic coma).
Pulmonary oedema (due to osmolarity changes or myocardial failure).
Cardiac arrhythmia (due to hyperkalemia, hypokalemia or hypocalcemia).

Chronic complications

Growth retardation and delayed puberty.
Epilepsy: The incidence in diabetic children is 10% (normal incidence is 0.5%).
Impaired intellectual capacity and school performance.
Peripheral neuritis (sensory loss, areflexia).
Vascular complications: Nephropathv, retinopathy.

Type I diabetes is not a benign disease. Life expectancy of diabetic children is only two thirds that of general population.

Coma in diabetic child is the most common acute complication, which can be fatal in up to 10% of cases. Detailed history of insulin dosage, preceding exercise and concurrent infection are essential and urgent investigations to identify the type are important.

Urgent investigations in comatose diabetic child

Blood sugar level and ketones in blood.
Blood gases for assessment of acid-base status.
Serum electrolytes (Na, K and Ca).
Calculation of serum osmolarity (see below).
Urine analysis for glucosuria and ketonuria.

- **Serum osmolarity** (in mOsm/kg H_20) = 2 (Na + K) + (glucose/18) + (urea/3)
  (Normal serum osmolarity is 275 - 295 mOsm/kg H_20)
- **Effects of hyperosmolarity:**
  * At 310 mOsm/liter, cerebral edema occurs.
  * At 340 mOsm/liter, renal failure occurs.
  * At 370 mOsm/liter, cellular disruption and systemic acidosis.

According to the results of investigations, 3 types of coma are identified

1. Hyperglycemic ketoacidotic coma: It is the commonest type, which is usually precipitated by infections or insulin underdosage. The clinical triad of dehydration, acidotic breathing and coma is characteristic. Laboratory diagnosis depends on the presence of hyperglycemia (above 300 mg/dl), ketonemia, metabolic acidosis, glucosuria and ketonuria. ***Cerebral edema*** with progressive deterioration of the level of consciousness may occur as a complication of rapid therapy (slow correction of dehydration and hyperglycemia is important to avoid cerebral edema).

2. Hyperglycemic hyperosmolar nonketotic coma: It is uncommon but serious type of coma with a high mortality rate. It is characterized by marked hyperglycemia (blood glucose above 600 mg/dl), hyperosmolarity (above 350 mOsm/kg H_2O) but without ketosis or acidosis (a degree of nonketotic acidosis may be present). Clinically, severe dehydration, coma and other neurological manifestations (convulsions, hemiparesis) are usually present. The degree of coma is directly related to the degree of hyperosmolarity. It is important to emphasize that this type of coma is not peculiar to diabetes and it can occur in several other conditions.

Causes of hyperglycemic hyperosmolar nonketotic coma (HHNC)

Disease states

- Head trauma (due to increased endogenous catecholamines and corticosteroids).
- Severe infection and dehydration.
- Diabetes mellitus.

Iatrogenic causes

- Drugs: Catecholamines, corticosteroids. diazoxide, phenytoin.
- Total parenteral nutrition.
- Suprasellar surgery.

3. Hypoglycemic coma: It is a major complication of insulin therapy. It is usually precipitated by insulin overdosage or increased exercise without corresponding reduction in insulin dosage. Fasting or reduction in diet without corresponding reduction in insulin dosage is also an important cause. Clinically, sweating and convulsions may occur. Blood sugar level is usually below 50 mg/dl. It responds dramatically to intravenous glucose 10%.

Causes of hypoglycemia

Hormonal causes

- Hormonal excess: Hyperinsulinism due to beta cell tumor or hyperplasia.
- Hormonal deficiency: Growth hormone, thyroxine or Adrenocortical deficiency.

Metabolic causes

- Carbohydrates: Glycogenosis type I, galactosemia.
- Aminoacids: Maple syrup urine disease, propionic acidemia.

Caloric disorders

- Inadequate intake: Starvation. malabsorption, protein calorie malnutrition.
- Excessive utilization: Severe exercise, fever, cold, renal glucosuria.

Drug-induced hypoglycemia

- Insulin overdosage or overdosage of oral antidiabetic agents.
- Salicylate poisoning, propranolol overdosage.

Ketotic hypoglycemia

- It is the most common cause. Age of onset is between 1- 5 years.
- Hypoglycemia occurs in attacks and is associated with ketonuria.

2. Hypothyroidism

Congenital hypothyroidism	Acquired hypothyroidism
Aplasia, hypoplasia or ectopia	Chronic lymphocytic thyroiditis
Dyshormonogenesis	Thyroidectomy or irradiation
Maternal goitrogen drugs	Goitrogen drugs (iodides, thiouracil)
Iodine deficiency	Infiltrative disease (cystinosis)
With hypopituitarism	With hypopituitarism

Next to diabetes, hypothyroidism (deficient production of thyroid hormone) is the commonest endocrinal disorder in children. The general incidence of congenital hypothyroidism is about 1/4000. Acquired hypothyroidism is probably twice as common as congenital hypothyroidism.

1. What are the clinical presentations?

The most important point in diagnosis of hypothyroidism is to make an "early diagnosis" before the mentality becomes greatly affected (it is not useful to diagnose a classic case of cretinism with coarse features and severe mental retardation).

Clinical presentations of hypothyroidism depend on the type and the age of the patient. Congenital hypothyroidism usually presents in neonatal period or early infancy while acquired hypothyroidism is mostly seen in school age children. ***Neonatal screening program*** is currently available in Egypt where all neonates are screened for congenital hypothyroidism. As errors may occur, high index of suspicion is important.

Clinical situations in which hypothyroidism should be suspected

In neonatal period

- Positive family history of previously affected sibling or maternal goiter.
- Prolonged gestational age or high birth weight.
- Prolonged physiological jaundice (persisting for more than 2 - 3 weeks).
- Feeding difficulties (lack of interest, choking spells) and poor activity.
- Cold mottled skin and constipation.

In infancy

- Delayed motor development (delayed head support, delayed sitting).
- Delayed mental development (delayed smiling, laughing, recognition of mother).
- Coarse features (large head, coarse hair with low anterior hair line, swollen eye lids, depressed nasal bridge, thick protruded tongue).

In childhood

- Short stature and slow growth velocity.
- Goiter (thyroid enlargement).
- School underachievement and poor learning ability.

2. What are the diagnostic investigations?

With clinical suspicion of hypothyroidism the following investigation are necessary for diagnosis.

1. Radiological assessment of bone age: It is a simple screening test. Delayed bone age is very suggestive especially when clinical suspicion is also present. In neonatal period, simple plain x-ray on the region of knee joint is very useful. Absent tibial and femoral epiphyses, which are normally present, is very suggestive of congenital hypothyroidism (see Basic Pediatric Radiology).

2. Serum level of thyroid hormones: Low serum levels of T4 and T3 is diagnostic of hypothyroidism (T4 level below 6 mcg/dl is diagnostic). Normal level of T4 is 9 - 18 mcg/dl in neonates and 7 - 15 mcg/dl in infants and children.

3. Serum level of thyroid stimulating hormone (TSH): High levels above 50 or even 100 microunit/ml usually occur in primary hypothyroidism. Normal level is below 10 microunit/ml. In secondary and tertiary hypothyroidism, the level of TSH is low.

Types of hypothyroidism

Primary hypothyroidism: Due to thyroxin deficiency.
Secondary hypothyroidism: Due to thyroid stimulating hormone (TSH) deficiency.
Tertiary hypothyroidism: Due to thyrotropin releasing hormone (TAH) deficiency.

3. What is the cause?

1. Congenital hypothyroidism: It is usually detected in neonatal period or infancy. Examination of the thyroid gland is clinically important to classify it into sporadic cretinism and goitrous cretinism.

a) Sporadic cretinism: It accounts for at least 90% of cases. It is due to aplasia, hypoplasia or ectopic gland. *Technetium thyroid scan* is very useful and can demonstrate the absent uptake (in aplasia and hypoplasia) or the abnormal location (in ectopic gland).

b) Goitrous cretinism: It accounts for only 10% of cases. It is caused by a defect in synthesis of thyroid hormone (dyshormonogenesis), maternal drugs or iodine deficiency. *Technetium thyroid scan* reveals increased uptake in case of dyshormonogenesis.

2. Acquired hypothyroidism: Most cases are discovered in school age children. *Chronic lymphocytic thyroiditis* (Hashimoto disease) is by far the commonest cause. It is an autoimmune disease and its diagnosis can be confirmed by the presence of circulating thyroid autoantibodies. The disease can be associated with other endocrinal deficiencies as Addison disease and diabetes mellitus (Schmidt syndrome or multiple endocrinal deficiency syndrome).

3. Adrenocortical Disorders

Adrenocortical insufficiency	Adrenocortical hyperfunction
Acute suprarenal failure	Congenital adrenal hyperplasia (excess androgens)
Infections (septicemia)	Cushing syndrome (excess cortisol)
Adrenal hemorrhage	Hyperaldosteronism (excess aldosterone)
Sudden withdrawal of steroids	Adrenal tumors
Chronic insufficiency	Virilizing tumors (excess androgens)
Addison disease	Feminizing tumors (excess estrogens)

Adrenal cortex secretes three groups of steroids; (1) glucocorticoids (cortisol) (2) mineralocorticoids (aldosterone) and (3) androgens (testosterone). Disorders of adrenal cortex are either hypofunction or hyperfunction and each can be congenital or acquired.

A) ADRENOCORTICAL INSUFFICIENCY

Adrenocortical insufficiency can be congenital or acquired and acute or chronic.

1. Acute suprarenal failure: It is a serious life threatening condition, which can lead to death if not urgently recognized and treated. In neonatal period, congenital adrenal hyperplasia (especially the salt losers group), sepsis and adrenal hemorrhage are the main causes. In infants and children, Waterhouse-fredrichsen syndrome (septicemia and adrenal hemorrhage as in memingococcemia), sudden withdrawal of prolonged steroid therapy and Addisonian crisis (episode of acute failure in Addison disease) are the main causes.

- ***Clinically***, manifestations of both cortisol deficiency (vomiting and hypotension) and aldosterone deficiency (dehydration, hypovolemia, and shock) are present. In neonates, manifestations usually occur at the age of 2 weeks (vomiting, dehydration and shock in a neonate should always raise suspicion).

- ***Laboratory findings*** include hypoglycemia (cortisol deficiency), metabolic acidosis, hyponatremia and hyperkalemia (aldosterone deficiency).

2. Addison disease: This autoimmune disease is the commonest cause of chronic adrenal insufficiency. It may be associated with other endocrinal diseases as diabetes, thyroiditis, hypoparathyroidism and hypogonadism (autoimmune polyendocrinopathy).

- ***Clinically***, the onset is often gradual and is characterized by muscle weakness, anorexia, vomiting, weight loss and orthostatic hypotension. Hyperpigmentation of the skin (due to ACTH excess) may occur later. Early the condition can be confused with infection but chronicity of symptoms should suggest the diagnosis.

- ***Laboratory findings*** include hypoglycemia (cortisol deficiency), metabolic acidosis, hyponatremia and hyperkalemia (aldosterone deficiency).

A) ADRENOCORTICAL HYPERFUNCTION

The most important 3 causes of hyperfunction are:

1. Congenital adrenal hyperplasia: This autosomal recessive disorder is caused by enzymatic defect in biosynthesis of cortical steroids. The enzymatic block leads to cortisol and aldosterone deficiency, excess ACTH, adrenal hyperplasia, excess intermediary metabolites and excess androgens. There are several enzymatic defects but the most important are 21 hydroxylase deficiency (90% of all cases), 11 hydroxylase deficiency and 17 hydroxylase deficiency.

• ***Clinically,*** manifestations are mainly related to deficient aldosterone and excess androgens and usually vary with the enzymatic defect;
- 21 hydroxylase deficiency causes aldosterone deficiency (salt losing manifestations as vomiting, dehydration, shock) and excess androgen (virilization of external genitalia).
- 11 hydroxylase and 17 hydroxlase cause hypertension (excess desoxycorticosterone) and excess androgen (virilization of external genitalia).

Diagnosis in females is easier because excess androgens cause ambiguous genitalia but in males, virilization is not clearly evident (see intersex and ambiguous genitalia).

• ***Laboratory findings*** include metabolic acidosis, hyponatremia and hyperkalemia (aldosterone deficiency) and excess urinary 17 ketosteroids (excess androgens).

2. Cushing syndrome: It is a characteristic pattern of obesity associated with hypertension due to cortisol excess. The main causes are adrenal hyperplasia (adrenal, pituitary or hypothalamic origins), adrenal tumors (adenoma or carcinoma) and prolonged steroid therapy (iatrogenic Cushing).

• ***Clinically,*** *obesity* is present in every case. It is more in the trunk and face (moon face) and servicodorsal area (buffalo hump). *Skin changes* also occur and include purplish stria mainly on flanks and lower abdominal wall, flushing and echymosis, pigmentation (excess ACTH) and virilization (acne, hirsutism, premature appearance of sexual hair). *Other features* include hypertension, headache and muscle weakness.

• ***Laboratory findings*** include hyperglycemia, polycythemia, eosinopenia and lymphopenia. Absent diurnal variation of plasma cortisol level is highly suggestive.

3. Hyperaldosteronism: This condition of excess aldosterone secretion can be primary (adrenal origin) or secondary (extraadrenal). Primary hyperaldosteronism is characterized by low rennin level and mainly caused by adrenal hyperplasia and adrenal tumors. Secondary hyperaldosteronism is characterized by high rennin level and mainly causes by congestive heart failure, nephrotic syndrome, liver cirrhosis, renovascular hypertension and Bartter syndrome.

• ***Clinically,*** *hypertension* (headache, irritability) and *chronic hypokalemia* (muscle weakness, polyuria, polydipsia) are the main manifestations. Severe hypokalemia may lead to intermittent paralysis and tetany (without low calcium level).

• ***Laboratory findings*** include hypokalemia, high aldosterone level. Plasma rennin is low in primary cases and high in secondary cases.

4. Intersex (Hermaphroditism)

46 XX- intersex (verilized female)	46 XY- intersex (undervirilized male)
Congenital adrenal hyperplasia	Defect in testicular differentiation
Maternal virilizing tumor (ovarian, adrenal)	Defect in testosterone synthesis
Maternal virilizing drugs	Defect in testosterone action
With other congenital anomalies	With other syndromes

True gonadal intersex results from failure of differentiation

Intersex (formerly known as hermaphroditism) means a *discrepancy between the morphology of gonads and external genitalia*. In true gonadal intersex, both gonads are present (ovaries and testes) while in 46-XX intersex (verilized female) and 46-XY intersex (undervirilized male), only one type of gonads is present (ovaries or testes).

Characteristic features of different types of intersex

Type	Chromosomes	Gonads	External genitalia
46 XX- intersex (verilized female)	XX	Ovaries	Ambiguous
46 XY- intersex (undervirilized male)	XY	Testes	3 presentations
True gonadal intersex	XX,XY	Ovotestes	Ambiguous

- In 46 XY- intersex (undervirilized male), the morphology of the external genitalia depends on the degree of differentiation. Three possibilities are present:
  1. Incomplete virilization (small phallus, small testes, ± undescended testes).
  2. Ambiguous genitalia (small phallus, bifid scrotum).
  3. Complete feminization (external genitalia of female in a male patient).

A) AMBIGUOUS GENITALIA

Ambiguous genitalia is a genitalia in which the sex cannot be identified. It is a medical emergency requiring urgent and appropriate measures to identify the true sex. Parents can be told that the baby is either a *"female with overdeveloped genitalia"* or *"male with underdeveloped genitalia"*. Birth certificate should not be filled out until the sex is identified and parents should not be encouraged or allowed to give the baby a neuter name. Ambiguous genitalia can result from one of 3 possibilities:

1. 46 XX- intersex (verilized female): The genitalia is ambiguous due to over-development by excess androgens (clitoral hypertrophy and labioscrotal fusion).

2. 46 XY- intersex (undervirilized male): The genitalia is ambiguous due to under-development by androgen deficiency (small phallus and bifid scrotum).

3. True gonadal intersex: The genitalia is ambiguous due to failure of differentiation

Diagnostic approach of ambiguous genitalia

Clinical evaluation

- Examine the mother for features of virilization (tumor, drugs).
- Search for gonads in labioscrotal folds and inguinal canal: Present gonads indicate a male sex but absent gonads does not exclude the possibility of undervirilized male.
- Search for multiple congenital anomalies: Ambiguous genitalia can be a part of multiple congenital malformations.

Diagnostic investigations

- Chromosomal analysis: To identify the chromosomal sex (Genotype).
- Ultrasound genitogram for presence of mullerian structures (vagina, uterus).
  - Normal mullerian structures: 46-XX intersex (or overvirilized female).
  - Absent or abnormal mullerian structures: 46-XY intersex or true gonadal intersex
- Investigations in 46-XX intersex (or virilized female).
  - 17 ketosteroids in urine: Increased in congenital adrenal hyperplasia and normal in maternal virilization due to drugs or tumors.
- Investigations in 46-XY intersex and true gonadal intersex
  - Hormonal studies: Testosterone and dihydrotestosterone levels before and after stimulation with human chorionic gonadotropins.
  - Gonadal biopsy: From palpable gonads or with surgical exploration

1. 46-XX intersex (or virilized female): Chromosomal analysis reveals XX and ultrasound genitogram reveals normal mullerian structures (vagina, cervix and uterus). Measurement of 17 ketosteroids in urine is useful in differentiation between congenital adrenal hyperplasia and maternal virilization.

2. 46-XY intersex (or undervirilized male): Chromosomal analysis reveals XY and ultrasound genitogram reveals absent or abnormal mullerian structure (vagina only without uterus). Hormonal studies and testicular biopsy are important to identify the responsible defect.

a) Defects in testosterone synthesis: In this group, *testosterone level is low.* Affected male may have a salt-losing manifestations (as in 3 beta hydroxysteroid dehydrogenase deficiency) or hypertension (in 17 hydroxylase deficiency). In 17 ketosteroid reductase deficiency, the level of 17 ketosteroids is increased in urine. These patients with defects in testosterone synthesis should be reared as females.

b) Defects in testosterone action: In this group, *testosterone level is normal.* The main 2 causes are:

- *5 alpha reductase deficiency (Type 3):* It is an autosomal recessive disease. Pelvic ultrasound reveals absent mullerian structures and prostate can be demonstrated. The testes are present in the inguinal canal or labioscrotal folds. These patients should be reared as males because at puberty normal virilization and height, phallus enlargement and spermatogenesis occur. Gynecomastia does not occur and beard growth is scanty. There are 5 phenotypes; type 1 (completely male), type 2 (male with micropenis), type 3 (ambiguous genitalia), type 4 (partial female) and type 5 (complete female).

• *Partial androgen insensitivity syndrome (Partial AIS):* This disease (formerly known as incomplete testicular feminization) is an x-linked disease. Pelvic ultrasound reveals blindly ended vagina (without uterus). The testes can be intra-abdominal or in inguinal canal. These patients should be reared as females because at puberty feminization occurs with breast enlargement and pubic and axillary hair. Moreover, in these patients it is easier to reconstruct the external genitalia to create a functional female (with vagina only) than to create a functional male phallus.

3. True gonadal intersex: Chromosomal analysis (genotype) reveals XX, XY or mosaicism. Pelvic ultrasound usually reveals some mullerian structures. Diagnosis is established by gonadal biopsy, which demonstrates the *presence or both gonads* (ovary in one side and testis on the other side or bilateral ovotestes).

B) INCOMPLETELY VIRILIZED MALE

In this group of intersex, the external genitalia is clearly a male genitalia but with a small phallus (micropenis) and a small or undescended testes. The main causes are:

1. 5 alpha reductase deficiency (Type II): Testosterone level is normal.
1. Hypopituitarism: Assess growth hormone.
2. Klinefelter syndrome: Chromosomal analysis reveals XXY.
3. Other syndromes As Reifenstein syndrome and Smith-Lemli-Opitz syndrome.
4. Idiopathic: No associated chromosomal or morphological abnormalities.

C) COMPLETELY FEMINIZED MALE

In this group, the male patient is wrongly identified and reared as a female because the external genitalia is that of normal females. The condition *should be suspected in any female with* (1) testes or mass in the labioscrotal folds, (2) inguinal hernia or mass in the inguinal canal and (3) primary amenorrhea. In these situations, chromosomal analysis will identify the true sex (male with XY). However, these patients should be reared as females because the external genitalia is already a female genitalia. The main causes are:

1. Complete androgen insensitivity syndrome (AIS): This disease (formerly known as testicular feminization syndrome) is the most common cause of 46-XY intersex. It is an x-linked disease with extreme failure of virilization. The external genitalia is that of normal female. Testes are usually intra-abdominal but may descend to inguinal canal. At puberty, there is a normal development of breasts but sexual hair is absent and menstruation does not occur (primary amenorrhea).

2. 5 alpha reductase deficiency (type 5): This disease is also characterized by normal testosterone level and needs to be differentiated from AIS.

3. XY pure gonadal dysgenesis: This disease (Swyer syndrome) of defective testicular differentiation is characterized by low testosterone level. Affected patients are female phenotype (female genitalia) with vagina, uterus and fallopian tubes. At puberty, breast development and menstruation do not occur.

5. Precocious Puberty

True precocious puberty	Precocious psuedopuberty
Idiopathic or constitutional 90% of cases in females 50% of cases in male **Organic diseases** Brain tumours Postencephalitis Gonadotropin therapy McCune Albright syndrome With hypothyroidism **Partial precocious puberty** Premature thelarche Premature adrenarche Premature menarche	**In females** **Isosexual (Feminization)** Ovarian tumors Exogenous estrogens **Heterosexual (Virilization)** Congenital adrenal hyperplasia Exogenous androgens **In males** **Isosexual (Musculinization)** Testicular tumors Exogenous androgens **Heterosexual (Feminization)** Adrenocortical tumors Exogenous estrogens

Precocious puberty is the early appearance of secondary sexual characters. These secondary sexual characters can be isosexual (feminization in females or musculinization in males) or heterosexual (virilization in females or feminization in males).

Clinical criteria for diagnosis of precocious puberty

In females

- Breast enlargement before the age of 8 years.
- Pubic or axillary hair before the age of 9 years.
- Menarche before the age of 10 years.
- Viritizing manifestations at any age.

In males

- Enlarged testes (more than 2 cm in greatest length) before 9 years.
- Enlarged penis (more than 7 cm in stretched length) before 10 years.
- Feminizing manifestations at any age.

In both males and females

Other associated findings, which are disproportionate to age as:
- Change in voice
- Facial hair
- Pigmented sexual organs.

• **In true precocious puberty,** gonadotropin level is high (gonadotropin dependant) and gonads are enlarged (testes in males, ovaries in females). Spermatogenesis occurs in males and ovulation occurs in females. True precocious puberty is always isosexual.

• **In precocious pseudopuberty,** the gonadotropin level is low (gonadotropin independent) and gonads do not enlarge. Spermatogenesis or ovulation does not occur. It can be either isosexual or heterosexual.

• **In partial precocious puberty,** only one isolated manifestation of puberty appears as breast enlargement (premature thelarche), pubic hair appearance (premature adrenarche) or menses (premature menarche). In all these conditions, other secondary sexual characters are absent and gonadrotropins are low.

Clinical presentations and diagnostic significance of precocious puberty

Females with breast enlargement before 8 years
- True precocious puberty (high gonadotropins).
- isosexual precocious pseudopuberty (low gonadotropins, high estrogens).
- Premature thelarche (breast enlargement only without enlarged labia).

Females with pubic hair before 9 years
- True precocious puberty (high gonadotropins).
- Heterosexual precocious pseudopuberty (low gonadotropins, high testosterone)
- Premature adrenarche (pubic hair only without clitoral hypertrophy).

Females with menses before 10 years
- True precocious puberty (high gonadotropins).
- Premature menarche (low gonadotropins)

Males with enlarged penis and testes
- True precocious puberty (high gonadotropins)

Males with enlarged penis only
- Isosexual precocious pseudopuberty.

- **In true precocious puberty,** exclusion of brain tumors by CT is essential. This is particularly important in males where organic diseases account for 50% of cases. In females 90% of cases are idiopathic and CT scan is normal.
- **In precocious pseudopuberty,** exclusion of ovarian tumors (in female isosexual), adrenal tumors (in female heterosexual) and testicular tumors (in male isosexual) is essential. CT scan or MRI of the abdomen and pelvis is important.
- **Partial precocious puberty** (also known as normal variants) is a benign condition, which usually regresses spontaneously and puberty usually occurs at the normal age.
  1. Premature thelarche usually occurs at 1 - 3 years.
  2. Premature adrenarche usually occurs at 6 8 years.
  3. Premature menarche is characterized by only 1 - 3 episodes of bleeding.

13

Genetic Disorders

- Genetic Disorders.

1. Chromosomal Disorders.
2. Metabolic Diseases.

Genetic Disorders

Chromosomal disorders	Multifactorial disorders	Single gene disorders
Numerical abnormalities	**Birth defects**	**Metabolic diseases**
Autosomal	Congenital heart disease	Aminoacids
Trisomies	Neural tube defects	Carbohydrates
Monosomies	Cleft lip, cleft palate	Lipids
Sex chromosomes	Pyloric stenosis	Mucopolysaccharides
Trisomies	**Midlife disorders**	**Systemic diseases**
Monosomies	Hypertension	Blood diseases
Structural abnormalities	Diabetes mellitus	Renal diseases
Deletions	Coronary heart disease	Endocrinal diseases
Translocations	Hyperlipidemia	Neurological diseases
Inversion	Peptic ulcer	Skeletal diseases

- **Chromosomal disorders:** Each human normally has 22 pairs of ***autosomes*** and one pair of ***sex chromosomes*** (XX in female and XY in male). Chromosomal diseases result from either numerical or structural abnormalities of chromosomes. The general incidence of chromosomal diseases is about 5/1000 (0.5%). *The recurrence risk is low (less than 1%).*

- **Multifactorial disorders:** These disorders are caused by a combination of genetic liability and environmental (nongenetic) factors. The general incidence of most multifactorial disorders is about 1/1000. *The recurrence risk is about 2- 5%* and it is higher when the defect is severe (e.g. recurrence risk of cleft lip and cleft palate is more than cleft lip alone).

- **Single gene disorders:** Each human normally has between 30,000 and 50,000 ***genes*** that are packaged in the 46 chromosomes. All genes come in pairs except for the genes of sex chromosomes of males. There are over 3000 different single gene disorders fortunately most of them are rare. The recurrence risk depends on the mode of inheritance, which can be autosomal recessive, autosomal dominant or x-linked. Generally, *the recurrence risk is very high (25 - 50%).*

a) Autosomal recessive disorders: The mutant gene is carried by *both asymptomatic parents* to affect 25% of their children. So, the recurrence risk is 25%. This mode of inheritance has a strong relation to consanguineous marriage.

b) Autosomal dominant disorders: The mutant gene is usually carried by a *one diseased parent* to affect 50% of his or her children. So, the recurrence risk is 50%. It is important to mention that several autosomal dominant diseases represent new mutations and appear in children of normal parents.

c) X-linked disorders: The mutant gene is carried by the *asymptomatic mother* to affect 50% of her sons. So, the recurrence risk is 50% in male offsprings. The mother also transmits the trait to 50% of her daughters to be carriers (as their mother).

Modes of inheritance of some single gene disorders

Autosomal recessive	Autosomal dominant	X-linked
Aminoacidopathies	Congenital spherocytosis	Fragile X syndrome
Galactosemia	Achondroplasia	G6PD deficiency
Glycogen storage diseases	Marfan syndrome	Hemophilia A, B
Lipidoses	Osteogenesis imperfecta	Wiskott-Aldrich syndrome
Mucopolysaccharidoses	Neurofibromatosis	Duchenne muscular dystrophy
Cystic fibrosis	Tuberus sclerosis	Becker muscular dystrophy
Wilson disease	Huntington chorea	Chronic granulomatous disease
Werdnig-Hoffmann disease	Periodic paralysis	Lesch-Nyhan syndrome
Ataxia telangiectasia	Hypercholesterolemia	Hunter syndrome (MPS, II)
Adrenal hyperplasia	Polycystic kidney	Color blindness

- **Fragile X syndrome** is recently recognized as a common cause of mental retardation in males. The general incidence of this x-linked form of mental retardation is 1/1000 males. Diagnosis depends on detection of a chromosomal marker called a fragile site on the distal end of the long arm of X chromosome.

Accurate diagnosis of genetic disorders is important for 3 reasons:

1. For the patient: Some genetic diseases can be largely controlled by:

* Simple dietetic measures As in phenylketonuria and galactosemia.
* High vitamin therapy: As in homocystinuria.
* Avoidance of exposure to certain foods and drugs: As in G6PD deficiency.
* Drug therapy: As in Wilson disease

2. For siblings: Early diagnosis can be made. This is particularly important in treatable conditions especially Wilson disease where early therapy can prevent liver damage.

3. For parents: Parents usually ask about the possibility of recurrence in subsequent pregnancies. With accurate diagnosis, precise genetic counseling can be offered. Again, the recurrence risk is less than 1 % in chromosomal disorders, 2 - 5% in multifactorial disorders and at least 25% in single gene disorders.

1. Chromosomal Disorders

Autosomal disorders	Sex chromosome disorders
Common autosomal trisomies	**Common sex chromosome disorders**
Trisomy 21 (incidence 1/700)	Klinefelter syndrome (incidence 1/1000)
Trisomy 18 (incidence 1/4000)	Poly-Y male (incidence 1/1000)
Trisomy 13 (incidence 1/6000)	Poly-X female (incidence 1/1000)
Other autosomal disorders	Turner syndrome (incidence 1/10.000 female)
Other trisomies (8, 9)	**Other sex Chromosome disorders**
Monosomies (21, 22)	Fragile X syndrome (incidence 1/1000)
Deletions (4, 5,9,11,13,18,21,22)	Atypical sex chromosome karyotype

Accurate clinical diagnosis of chromosomal disorders can be very difficult even to experts. Although some chromosomal disorders have quite peculiar features and can be easily recognized (trisomy 21, trisomy 18, trisomy 13, Turner syndrome), most other disorders do not present with a clear characteristic features. Moreover, several single gene disorders and morphological syndromes can present with clinical features that can be easily confused with chromosomal disorders. From the clinical point of view, it is not important for physicians to reach an accurate diagnosis, but it is very essential to know ***"how to suspect a chromosomal disease"***.

Clinical situations suspecting chromosomal disorder

Dysmorphic or abnormal features

Odd-looking face, coarse features, mongoloid features.
Eyes Mongoloid or antimongoloid slanting, hypotelorism or hypertelorism.
Ears: Malformed or large ears, low-set ears.
Mouth and mandible: Cleft lip and palate, micrognathia (receding mandible).
Hands: Simian crease, clinodactyly, polydactyly, clenched fist.
Feet: Gap between 1st and 2nd toe, rockerbottom, abnormal creases.

Mental retardation

All children with unexplained retardation should have chromosomal analysis.

Ambiguous genitalia

All newborns with ambiguous genitalia should have chromosomal analysis.

Delayed puberty

Klinefelter syndrome (in males) and Turner syndrome (in females) are important causes of delayed puberty. Androgen insensitivity syndrome (AIS) is also important (see intersex).

- It is important to realize that abnormal facial features are not peculiar to chromosomal diseases and they can be caused by several genetic or even nongenetic diseases.

Causes of odd-looking face

Chromosomal disorders

Trisomy 21: Mongoloid slanting, medial epicanthal fold, protruded tongue.
Trisomy 18: Small features, low-set malformed ears, prominent occiput.
Trisomy 13: Coarse features, low-set malformed ears, median cleft lip and palate.
Several other disorders.

Single gene disorders

Aminoacidopathies: Phenylketonuria (blond, fair hair, blue eyes).
Mucopolysaccharidoses: Coarse features
Hurler-like disorders: Coarse features.

Endocrinal disorders

Hypothyroidism: Coarse features.
Hypoparathyroidism (Di George syndrome): Antimongoloid stant, low-set ears.
Infant of diabetic mother: Rounded plumby face

Maternal drug ingestion

Fetal alcohol syndrome: Short palpebral tissue, short upturned nose.
Dilantin syndrome.
Androgens.

Other disorders with peculiar face

Idiopathic hypercalcemia (William syndrome): Elfin face, aortic stenosis.
Progeria: Senile face and alopecia.
Silver syndrome: Triangular face.
Mobius syndrome: Expressionless face.

CHROMOSOMAL ANALYSIS

Once a chromosomal disease is suspected, chromosomal analysis is indicated for confirmation or exclusion. Study of chromosomes can be performed on any tissue in which cells are actively undergoing mitosis.

1. Peripheral blood study: It is the most commonly used study because blood is the easiest tissue to obtain. The ***T-cells*** are stimulated with phytohemagglutinin (PHA), which causes the cells to undergo mitosis. Results of analysis can be obtained after 4- 5 days (the time required by the cells to enter metaphase).

2. Bone marrow study: As bone marrow cells are constantly dividing, the result of analysis can be obtained within 6 hours of obtaining the sample. The main indication of chromosomal bone marrow study is leukemia.

3. Organ tissue study: Tissue biopsies (usually the skin) can be used for chromosomal studies when blood sample cannot be obtained (as in case of stillbirth) or when the diagnosis of mosaicism needs to be confirmed. In this case, results of analysis can be obtained after, at least, 3 - 4 weeks (the time needed for the cells to grow in culture).

Chromosomal karyotype is the term used for the "arrangement of chromosomes that is made from the photomicrographs". This arrangement allows the analysis of chromosome number and structure. The chromosomes are arranged in 7 groups (A to G) in order of decreasing size.

Chromosomal karyotype

A group: The 3 longest chromosomes (1, 2, 3)
B group: Chromosomes 4, 5
C group: Chromosomes 6 to 12 and the X chromosome
D group: Chromosomes 13, 14, 15
E group: Chromosomes 16, 17, 18
F group: Chromosomes 19, 20
G group: Chromosomes 21, 22 and the Y chromosome

• Chromosomal analysis should include a 'fragile X study' for detection of the fragile X syndrome. This syndrome is a common cause of mental retardation in males (see also x-linked disorders).

A) COMMON AUTOSOMAL TRISOMIES

1. Trisomy 21 (Down syndrome): It is the most common autosomal trisomy (1/700 live birth). It has 3 genetic patterns: nondisjunction (95% of cases), translocation (4%) and mosaicism (1%). The incidence of nondisjunction type rises dramatically with advanced maternal age (1/2000 at age 20, 1/1000 at age 30, 1/100 at age 40 and 1/10 at age 50). The recurrence risk is about 1% above the age-related risk.

• Clinical recognition of Down syndrome is not difficult even at birth. ***Characteristic dysmorphic features*** include upward slanting palpebral fissure, epicanthal folds, flat nasal bridge, malformed ears, protruded tongue, simian crease, clinodactyly and big space between first and second toe. The most constant features are the upward slanting of palpebral fissues and the big space between first and second toe (present in about 97% of cases). Simian crease is present in only 50-55% of cases. On the other hand, simian crease is present in about 4% of normal individuals (the chance that a newborn with simian crease has a Down syndrome is only 1 in 60). ***Associated congenital anomalies*** include congenital heart disease (in 40% of cases) and gastrointestinal anomalies (as duodenal atresia). ***Delayed motor development and mental retardation*** appear in infancy (mean IQ is 50).

• The main complications of Down syndrome are those related to the congenital heart disease, recurrent respiratory infections and the increased risk of leukemia (20 times commoner). In absence of a congenital heart disease, long-term survival is usual.

2. Trisomy 18 (Edward syndrome): It is the second most common autosomal trisomy (1/4000). It has 2 genetic patterns; nondisjunction (90% of cases) and mosaicism (10%). There is also a relation between advanced maternal age and the occurrence of trisomy 18 but it is less marked than that of trisomy 21 and trisomy 13.

• ***Characteristic dysmorphic features*** include low birth weight, microcephaly with prominent occiput, low-set malformed ears, micrognathia, clenched fist and rocker-bottom feet. ***Associated congenital anomalies*** include severe CNS malformations with severe mental retardation, congenital heart disease (in 60% of cases) and congenital hip dislocation.

• Prognosis is very poor. 30% of patients die in neonatal period and 90% die in infancy.

3. Trisomy 13 (Patau syndrome): It is the third most common autosomal trisomy (1/6000). It has 3 genetic patterns: nondisjunction (75%), translocation (20%) and mosaicism (5%). There is also a relation between the advanced maternal age and the occurence of trisomy 13 but it is less marked than that of trisomy 21.

• ***Characteristic dysmorphic features*** include low birth weight, microcephaly, coarse features (low anterior hair line, microphthalmia, hypotelorism, median cleft lip and palate), low-set malformed ears, polydactyly and rockerbottom feet. ***Associated congenital anomalies*** include severe CNS malformations (including holoprosencephaly) with severe mental retardation, congenital heart disease (80% of cases) and genital malformations.

• Prognosis is very poor. 50% of cases die in neonatal period and 90% die in infancy.

Features of the three most common autosomal trisomies

Feature	Trisomy 21	Trisomy 18	Trisomy 13
Eponym	Down syndrome	Edward syndrome	Patau syndrome
Incidence	1.700	1/4000	1/6000
Genetic patterns	Nondisjunction (95%) Translocation (4 %) Mosaicism (1%)	Nondisjunction (90%) Mosaicism (10 %)	Nondisjunction (75 %) Translocation (20%) Mosaicism (5%)
Birth weight	Normal	Low birth weight	Low birth weight
Face	Mongoloid slant Malformed ears	Small features Low-set ears	Coarse features Low-set ears
Hand	Simian crease Clinodactyly	Clenched fist Hypoplastic nails	Polydactyly Hyperconvex nails
Foot	Big space (1st, 2nd)	Rockerbottom	Rockerbottom
Cardiac defect	40%	60%	80%
CNS anomalies	No	Severe	Severe
Prognosis	Long term survival	90% die in infancy	90% die in infancy

B) AUTOSOMAL DELETION SYNDROMES

A deletion syndrome results from a deletion of a part of the short arm (p-) or long arm (q-) of a chromosome. Common features of deletion syndromes include low birth weight, microcephaly, mental retardation and dysmorphic features. Clinical different-tiation between various deletion syndromes can be only made by experts.

Some characteristic features of deletion syndromes

4 p –: Flat nasal bridge (Greek helmet face), beaked nose.
5 p –: (Cri du chat syndrome): Cat-like cry, round face, antimongoloid slant.
13 q –: Trigonocephaly, flat wide nasal bridge, ptosis.
18 p –: Hypertelorism, large floppy low-set ears, micrognathia.
18 q –: Carp-shaped mouth, protruding mandible.
21 q –: Antimongoloid slant, large or low-set ears, micrognathia.
22 q –: Epicanthal folds, ptosis, large or low-set ears.

C) SEX CHROMOSOME DISORDERS

1. Klinefelter syndrome (47, XXY male): It is a common chromosomal disorder of males (1/1000 male) characterized by gynecomastia, small atrophic testes and absent spermatogenesis (azoospermia). The basic chromosomal disorder is the presence of an extra X chromosome (47, XXY). Although affected males are usually taller than average, clinical manifestations usually do not appear before puberty (gynecomastia and absent spermatogenesis). Klinefelter syndrome is not a serious pediatric problem because, apart from infertility, most affected male lead normal lives. The degree of mental affection is related to the number of extra X chromosmes (48, XXXY in 3% of cases and 49, XXXXY in 1% of cases).

2. Poly-Y male (47, XYY male): It is a common chromosomal disorder of males (1/1000) characterized by aggressive antisocial behaviour and difficult personality problems in school years.

3. Poly-X female (47, XXX female): It is a common chromosomal disorder of females (1/1000) characterized by a minor degree of affection of motor, speech and mental development. The degree of mental affection is related to the number of extra X chromosomes (48, XXXX and 49, XXXXX in less than 2% of cases).

4. Turner syndrome (45, X female): It is a common chromosomal disorder of females (1/10,000) characterized by short stature, webbing of the neck, widely separated nipples, cubitus vulgus (increased carrying angle) and gonadal dysgenesis (primary amenorrhea). The condition can be suspected at birth when edema of the dorsum of hands and feet are present. Associated renal anomalies (40% of cases) and cardiac anomalies especially coarctation of aorta (20% of cases) may be present. It has 3 genetic patterns; monosomy 45, X (in 55% of cases), deletion or duplication (in 25%) and mosaicism (in 15%). When a girl suspected of having Turner syndrome has 46, XX karyotype in peripheral blood, 2 possibilities should be considered: (1) ***Mosaicism:*** Skin biopsy in necessary to find mosaicism in cultured fibroblasts, (2) ***Noonan syndrome:*** It is a non-chromosomal disease which has a superficial resemblance to Turner syndrome (webbing of neck, low posterior hair line, variable degree of hypogonadism and congenital heart disease, mostly pulmonary valvular stenosis). It occurs in *both males and females*. Undescended testes occur in 70% of affected males.

2. Metabolic Diseases

Aminoacid disorders (Aminoacidopathies)
- Phenylketonuria, tyrosinemia, homocystinuria
- Maple syrup urine disease, isovaleric acidemia, propionic acidemia
- Disorders of urea cycle (hyperammonemia)
- Other aminoacid disorders

Glycogen storage diseases (Glycogenoses)
- Liver disease (types 1, 3, 4, 6, 8, 9, 10)
- Muscle disease (types 5, 7)
- Cardiomyopathy (type 2 or Pompe disease)

Lipid storage diseases (Lipidoses)
- Hepatosplenomegayl (Gaucher disease, Niemann Pick disease)
- Skin manifestations (Farber disease, Fabry disease, Refsum disease)
- Neurological manifestations (as infantile Gaucher disease)

Mucopolysaccharidoses
- 9 types. Type 1 (Hurler disease) is the most severe type

Hurler-like disorders
- Mucolipidoses (3 types: ML-I, ML-II, ML-III).
- Gangliosidoses (3 types: GM-I, GM-II, GM-III).
- Glucoproteinoses (3 types: Mannosidosis, fucosidosis, aspartylglucosaminuria).

Full description of all metabolic diseases (several hundreds) is obviously beyond the scope of this book. Although each individual metabolic disease is rare, the hundreds of such diseases together are responsible for a significant amount of childhood illness. From the clinical point of view, it is not important for physicians to reach an accurate diagnosis but it is very essential to know ***"how to suspect a metabolic disease"***.

Clinical situations suspecting metabolic disease

Clinical presentation	Suspected metabolic disease
Neonatal convulsions, coma	Aminoacidopathies
Neonatal jaundice	Galactosemia, tyrosinemia
Vomiting and failure to thrive	Aminoacidopathies, galactosemia
Unusual odour of urine	Aminoacidopathies
Mental retardation	Aminoacidopathies, mucopolysaccharidoses
Episodes of metabolic acidosis	Aminoacidopathies, carbohydrate disorders
Liver disease or hepatomegaly	Glycogenoses, tyrosinemia, Wilson disease
Hepatosplenomegaly	Lipidoses, mucopolysaccharidoses
Coarse features	Mucopolysaccharidoses, Hurler-like disorders
Blond, fair hair, blue eyes, eczema	Phenylketonuria

A) AMINOACID DISORDERS (AMINOACIDOPATHIES)

Aminoacidopathies are a group of disorders of aminoacid metabolism caused by an enzymatic defect in the steps of catabolism of aminoacids. They are characterized by elevated plasma level of the involved aminoacid ***(aminoacidemia)*** and overflow into the urine of the involved aminoacid or related metabolites ***(aminoaciduria).*** Almost all disorders are inherited as an autosomal recessive disorders.

Most common aminoacid disorders

Involved aminoacid	Disorders
Aromatic aminoacids	
Phenylalanine	Phenylketonuria (1/10.000)
Tyrosine	Tyrosinemia, albinism, alkaptonuria
Sulphor-containing aminoacids	
Methionine	Homocystinuria (Marfan-like features)
Cysteine	Sulphate oxidase deficiency
Branched chain aminoacids	
Valine, leucine, isoleucine	Maple syrup urine disease, isovaleric acidemia, Propionic acidemia, methylmalonic acidemia
Other aminoacids	
Histidine, glycine, lysine, proline, tryptophan	Histidinemia, glycinemia, lysinemia, Prolinemia, tryptophanemia
Urea cycle disorders	
Hyperammonemia	Citrulinemia, argininemia, argininosuccinic acidemia
Aminoacid transport defect	
Cysteine (renal defect)	Cystinuria
Tryptophan (intestinal defect)	Hartnup disease, blue diaper syndrome

Clinical presentations

Diagnosis of aminoacidopathies should be made early and before the development of ***mental retardation,*** which occurs in most conditions if diagnosis is delayed. The main presentations, which should raise suspicion are:

1. Neonatal convulsions and coma: Vomiting, lethargy, convulsions and coma that appear after few days of milk intake should suggest an aminoacid disorder as phenylketonuria, organic acidemia (propionic acidemia or methylmalonic acidemia) or a disorder of urea cycle with hyperammonemia (see neonatal convulsions).

2. Neonatal jaundice: Tyrosinemia may present with a late onset conjugated hyperbilirubinemia. Simple ferric chloride urinary screening test is useful for diagnosis. Other metabolic diseases especialy galactosemia should be also considered.

3. Vomiting and failure to thrive: Persistent vomiting and failure to thrive in infancy should always suggest aminoacidopathies especially when associated with mental retardation or abnormal odor of urine. Phenylketonuria should be suspected when the infant is blond, with fair hair and blue eyes. Ferric chloride test is very useful for diagnosis.

4. Abnormal odor of urine: Several aminoacid disorders are associated with abnormal urine odor as phenylketonuria (mousy or musty), tyrosinemia (rancid or fishy), maple syrup urine disease (maple syrup), isovaleric acidemia and glutaric acidemia (sweaty feet).

5. Episodes of metabolic acidosis: Unexplained episodes of metabolic acidosis should suggest a metabolic disease as *aminoacidopathies* (maple syrup urine disease, isovaleric acidemia, propionic acidemia and methylmalonic acidemia) and disorders of *carbohydrate metabolism* (Von Gierke disease, pyruvate carboxylase deficiency and pyruvate dehydrogenase deficiency).

Laboratory diagnosis

With clinical suspicion of aminoacidopathies, laboratory investigations for confirmation or exclusion are indicated. There are both screening and diagnostic tests. ***Urinary screening tests*** are simple and very useful in suggesting several disorders. ***Diagnostic chromatography*** (by estimation of blood and urinary levels of aminoacids) is indicated in case of positive screening tests.

Urinary screening tests of aminoacid disorders

Ferric chloride test

2 drops of ferric chloride solution 2% + 1 ml urine. Normally, a purple colour appears and turns to red brown in 1 - 2 minutes. Abnormalities are:

- Green colour: Phenylkelonuria, tyrosinemia, histidinemia, maple syrup urine disease, ketotic hyperglycinemia, conjugated bilirubinuria.
- Yellow colour: Pyruvic acidemia, valinemia.
- Stable purple: Drugs as salicylates and paraaminosalicylic acid.
- Deep brown: Tryptophan load.

Cyanide nitroprusside test

1 ml solution A (5% sodium cyanide) + 2.5 ml urine. After 15 minutes, add 0.5 ml solution B (0.5% sodium nitroferricyanide).

- Appearance of pink colour suggests all types of cystinuria (including homocystinuria) or generalized aminoaciduria.

Ehrlich aldehyde test

1 ml Ehrlich reagent + 5 ml urine.

- Appearance of bink colour after 15 minutes occurs in presence of excess indoles (as in Hartnup diseases) or urobilinogen (porphyria).

B) GLYCOGEN STORAGE DISEASES (GLYCOGENOSIS)

Glycogen storage diseases (glycogenosis) are a group of autosomal recessive disorders caused by an enzymatic defect of the glycogenolytic activity and are characterized by a glycogen accumulation (storage) in the liver, heart or skeletal muscles. The main clinical presentations are:

1. Hepatomegaly: It is the main presentation of most types (1,3,4,6,8 and 9).

• ***Type I glycogenoses (Von Gierke disease):*** It is the most common type and it is characterized by: (1) *hepatomegaly* which may be detected even in neonatal period. (2) *hypoglycemia* which may lead to recurrent convulsions, (3) *hemorrhage* may occur due to platelet dysfunction, (4) *hyperlactic acidemia* with recurrent episodes of acute metabolic acidosis, (5) *hyperlipidemia* (high cholesterol level) and (6) *hyperuric acidemia* with marked elevation of serum uric acid level (normal value is 2 - 7 mg/dl). Affected children are often stunted, with "doll face" and normal mental development.

• In ***type III glycogenosis (Cori Forbes disease),*** moderate to marked hepatomegaly is present but without hypoglycemia, acidosis or hyperlipidemia.

• ***Type IV glycogenosis (Andersen disease)*** is characterized by hepatosplenomegaly, ascites, cirrhosis and liver failure. It is the only one causing hepatic damage.

• ***Types VI and IX*** are clinically similar to type III.

• In ***type VIII,*** hepatomegaly is accompanied by a progressive neurological disease (truncal ataxia and nystagmus).

Accurate differentiation between these types requires liver biopsy and study of the enzymatic defects.

2. Cardiomegaly: It is the presentation of ***type II (Pompe disease).*** It has 3 forms (1) *infantile form* characterized by cardiomegaly, hypotonia (floppy infant) and protruded tongue in neonatal period or early infancy (see cardiology), (2) *Childhood form* with cardiomegaly in childhood and (3) *adult form* (cardiomegaly in adulthood).

3. Muscular weakness: It is the presentation of ***type V (McArdle syndrome) and type VII***. Muscular spasms and muscle weakness are the main presentations. Muscle biopsy is essential for diagnosis.

C) LIPID STORAGE DISEASES (LIPIDOSES)

Lipid storage diseases (lipidoses) are a group of autosomal recessive disorders (except Fabry disease, x-linked) caused by enzymatic defects and characterized by *lysosomal storage of lipids*. Lipidoses are classified according to the stored substance.

Clinical presentations

1. Hepatosplenomegaly: Gaucher disease and Niemann Pick disease are the main causes of metabolic Hepatosplenomegaly. Other lipidoses as mucolipidoses, gangliosidosis and fucosidosis are also associated with hepatosplenomegaly but mental retardation and coarse Hurler-like features are the main presentations.

Classification of lipidoses

Disease	Stored lipid	Enzyme defect
Cerebroside storage		
Gaucher disease	Glucocerebroside	Glucocerebrosidase
Globoid leukodystrophy	Galactocerebroside	Galactocerebrosidase
Metachromatic leukodystrophy	Cerebroside sulphate	Arylsulphatase
Sphingomyelin storage		
Niemann Pick disease	Sphingomyelin, cholesterol	Sphingomyelinase
Ceramide storage		
Farber disease	Ceramide	Ceramidase
Fabry disease	Ceramide trihexoside	Galactosidase
Phytanic acid storage		
Refsum disease	Phytanic acid	Phytanoyl CoA oxidase
Cholesterol storage		
Wolman disease	cholesterol, cholesteryl esters	Acid lipase
Other lipidoses (Hurler-like disorders)		
Mucolipidoses (mucolipid storage)	(see Hurler-like disorders)	
Gangliosidosis (ganglioside storage)		
Fucosidosis (glycolipid storage)		

- Globoid leukodystrophy and metachromatic leukodystrophy are discussed with "spastic infant".

a) Gaucher disease is an autosomal recessive disease that has 3 types; *Type I (adult non-neuropathic form)* is the most common (99% of cases) and it usually presents in infancy with huge hepatosplenomegaly (spleen is always bigger). *Type II (infantile neuropathic form)* is characterized by splenomegaly and progressive neurological disease (convulsions and motor weakness). *Type III (Juvenile neuropathic form)* is intermediate form between types I and II. Diagnosis is confirmed by splenic biopsy or bone marrow examination, which reveals the characteristic Gaucher cells (large multinucleated cells with fibrillar nonvaculated cytoplasm).

b) Niemann Pick disease is an autosomal recessive disease that has 4 types; *type A* (visceral and early neurological manifestations), *type B* (visceral manifestations only), *types C and D* (visceral and late neurological manifestations). In all types, hepato-splenomegaly is present and the liver may be larger than the spleen. Vaculated lymphocytes in peripheral blood, if present, are characteristic of Niemann Pick disease. Bone marrow reveals the foam cells (not peculiar to Niemann Pick but also present in other lipidoses).

2. Cutaneous manifestations: ***Farber disease*** presents in infancy with subcutaneous nodules, hoarse cry (laryngeal involvement), arthropathy (synovial involvement). ***Fabry disease*** presents in *midchildhood* with purple nodular rash and painful joints. ***Refsum disease*** presents in *late childhood* with icthyosis, ataxia and peripheral neuritis. Fundus examination reveals retinitis pigmentosa.

Causes of metabolic hepatosplenomegaly

Without mental retardation

Gaucher disease: Characteristic Gaucher cells in bone marrow.
Niemann Pick disease: Foam cells in bone marrow.
Glycogenoses type IV: Ascites, cirrhosis and liver failure.
Osteopetrosis: Skeletal survey is diagnostic (marble bone disease).

With mental retardation

Mucopolysaccharidoses Mucolipidoses Gangliosidoses Glycoproteinosis	***Coarse hurler-like features***

- Argininosuccinic acidemia (aminoacid disoreder) can also cause hepatosplenomegaly.

3. Neurological manifestations: Progressive motor and mental retardation can be the presentation of some lipidoses as Type II and Type III Gaucher disease, types A, C, and D Nieman Pick disease, gangliosidosis and mucolipidoses.

Laboratory diagnosis

Accurate diagnosis and differentiation between different types of lipidoses requires enzymatic study of the cultured skin fibroblast. In diseases presenting with progressive neurological disease, brain biopsy is essential for diagnosis.

D) MUCOPOLYSACCHARIDOSES

Mucopolysaccharidoses are a group of autosomal recessive disorders (except Hunter disease, x-linked) caused by enzymatic defects and are characterized by (1) lysosomal storage of mucopolysaccharides, (2) excessive excretion of mucopolysaccharides in urine (mucopolysacchariduria), (3) multisystem involvement and progressive course after an earlier period of apparent normality.

There are 9 types. **Type I (MPS-I-H or Hurler disease)** is the most common and most severe form. It is characterized by an *onset at the age of 1 year* (after infancy) and a full picture at about 2 years. Death occurs at 6 - 10 years.

Other types of mucopolysaccharidoses differ from Hurler disease in the enzymatic defect, age of onset, clinical manifestations and prognosis. ***Scheie diseases*** (MPS-I-S) is the mildest form and is characterized by just corneal opacity and claw hand. The mentality is normal and it is not fatal. Scheie disease was originally the type V. Since its enzymatic defect is similar to that of Hurler disease, it is now known as type I-S. ***Hunter disease*** (MPS-II) differs from Hurler disease by its delayed onset and slower progression. There is no cloudy cornea and it is x-linked. ***Sanfilippo disease*** (MPS-III) is characterized by severe mental retardation and minimal findings (only cloudy cornea at 6 years). ***Morquio disease*** (MPS IV) is characterized by normal mentality, gait problems

Diagnostic criteria of Hurler disease (MPS-I-H)

Characteristic clinical features

Mental retardation.

Coarse features: Large head, depressed nasal bridge, persistent nasal discharge, large tongue, thick skin (grotesque face), and cloudy cornea.

Claw hand deformity, contractures of joints and short stature.

Hepatosplenomegaly.

Radiological skeletal manifestations of dysostosis multiplex

Several skeletal changes in the skull, chest, spine, pelvis, hands and wrist (see Basic Pediatric Radiology).

Mucopolysacchariduria

CTAB test: 6 drops of CTAB reagent + 1 ml urine gives cloudy flocculent precipitate in all types of mucopolysaccharidoses except Morquio.

Study of cultured skin fibroblast

Study of enzymatic activity of alpha L-ioduronidase.

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and skeletal changes in the form of short neck, short trunk, thoracic kyphosis and lumbar lordosis (barrel shaped chest). The picture is usually evident at 6 years. ***Maroteaux-Lamy disease*** (MPS-VI) differs from Hurler by its delayed onset, slower progression and normal mentality. ***Sly disease*** (MPS-VII) may have an earlier onset in infancy. PMS-VIII is no longer used. MPS-IX is characterized by periarticular soft tissue masses and short stature. Accurate diagnosis of these conditions depends on the *study of cultured fibroblast* and determination of the enzymatic defect characteristic of each disease.

E) HURLER-LIKE DISORDERS

Hurler-like disorders are groups of metabolic diseases characterized by clinical and radiological features similar to that of Hurler disease but without mucopolysacchariduria. These disorders are mucolipidoses, gangliosidosis and glycoproteinosis.

1. Mucolipidoses are characterized by lysomal storage of both mucopolysaccharides and sphyngolipids. There are 3 types:

a) Mucolipidosis type I (sialidosis): It is characterized by mild Hurler-like features cherry red spots in macula, foam cells in bone marrow and increased sialic acid in liver urine and fibroblasts. Recently, sialidosis is not included in mucolipidoses.

b) Mucolipidosis type II (I-cell disease): It is characterized by coarse cytoplasmic Inclusions in cultured fibroblast (I-cell refers to the Inclusions). It is characterized by severe Hurler-like features starting in neonatal period and gingival hyperplasia.

c) Mucolipidosis type III (Pseudo-Hurler polydystrophy): It is characterized by mild Hurler-like features in childhood.

2. Gangliosidosis are characterized by lysosomal storage of gangliosides. There are 3 types that differ in the age of onset and clinical manifestations.

Types of gangliosidosis

GM1:	**Type 1** (Generalized gangliosidosis): Early onset of Hurler-like features. **Type 2** (Juvenile gangliosidosis): Late onset of Hurler-like features.
GM2:	**Type 1** (Tay-Sachs disease): Blindness, cherry red macula. **Type 2** (SandHoff disease): Hepatosplenomegaly. **Type 3** (Juvenile Tay Sachs disease).
GM3:	**GM3 gangliosidosis:** Early onset.

3. Glycoproteinosis are characterized by lysosomal storage of glycoproteins. There are 3 diseases; mannosidosis (early onset of Hurler-like features), fucosidosis and aspartylglucosaminuria (late onset of Hurler-like features).

Differential diagnosis of Hurler-like features according to age of onset

In neonatal period or during infancy
- Mucolipidosis type II (I-cell disease).
- Generalized gangliosidosis (GM1, type 1)
- Mannosidosis
- Mucopolysaccharidosis, type VII.

In early childhood
- Hurler disease (MPS- I-H)
- Hunter disease (MPS- II)
- Maroteaux-Lamy disease (MPS- VI)
- Mucolipidosis type I (sialidosis)

In late childhood
- Scheie disease (MPS-I-S)
- Mucolipidosis type III (pseudo-Hurler polydystrophy).
- Fucosidosis.
- Aspartylglucosaminuria.

- Accurate differentiation between all these disorders requires study of cultured fibroblasts and determination of the enzymatic defect characteristic of each disease.

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Psychological Disorders

1. Eating disorders.
2. Sleep disorders.
3. Habit disorders.
4. Anxiety disorders.
5. Mood disorders.
6. Disruptive Behavioral disorders.
7. Neurobehavioral disorders.
8. Autism and Schizophrenia.

1. Eating Disorders

Rumination: Repeated regurgitation without nausea or gastrointestinal diseases.
Pica: Chronic ingestion of non-nutritive substances.
Bulimia nervosa: Recurrent episodes of binge eating followed by self-induced vomiting.
Anorexia nervosa: Severe anorexia due to intense fear of becoming obese.

Rumination is a problem of infancy while pica is usually affecting young children. Bulimia and anorexia nervosa are disorders of adolescent females.

1. Rumination: It is a rare disorder characterized by repeated regurgitation without nausea or gastrointestinal illness that usually leads to failure to thrive and weight loss. It is mostly seen between 3-14 months of age and mostly in males. Disturbed parent child relationship is often present. The condition is not benign as up to 25% of affected infants die. Differential diagnosis should include congenital gastrointestinal anomalies and pyloric stenosis.

2. Pica: It is a chronic ingestion of non-nutritive substances as plaster, charcoal, clay, wall paints, ashes and earth usually above the age of 2 years. The condition is commoner in patients with mental retardation and autism and in low socioeconomic classes. Persistent pica is usually associated with family disorganization, poor supervision and psychological neglect. Children with pica are at increased risk of lead poisoning, iron deficiency anemia and parasitic infestations. Therefore, they should be investigated for these conditions.

3. Bulimia nervosa (BN): It is a condition of adolescent females characterized by repeated episodes of *binge* eating (eating large amount of food in a short time during which the patient cannot stop eating), which is usually followed by self-induced vomiting or use of laxatives (*purge*) to counteract the effect of binge eating. Two episodes of *binge-purge pattern* per week for at least 3 months are necessary for diagnosis.

4. Anorexia nervosa (AN): It is also a disorder of adolescent females but much less common than bulimia. It is characterized by severe anorexia caused by intense fear of being obese and it does not diminish even with weight loss. It is usually associated with excessive movements in the face and denial of hunger. Clinical manifestations include both physical and psychological effects. *Physical effects* include weight loss, bradycardia and postural hypotension. *Psychological effects* include impairment of concentration and problem solving. Structural changes in the volume of gray and white matter occurs. Mortality rate is about 10% and it is usually due to severe electrolyte disturbance and cardiac arrhythmias. It is surprising to know that patients with anorexia nervosa have remarkable resistance to infections. This observation is supported by immunological studies and explained by several mechanisms including low estrogen level, low calcium level and high cotrisol level.

2. Sleep Disorders

Sleepwalking: Walking during the first third of night.
Nightmares: Attacks of screaming and fear during the last third of night.
Night terrors: Attacks of screaming and fear during the first third of night.
Narcolepsy: Sudden irresistible desire to sleep.
Restless legs syndrome: Uncomfortable sensations in lower limbs, relieved by movements.
Insomnia: Difficulty in initiation or maintenance of sleep.

1. Sleepwalking (somnambulism): It is a very common condition especially in toddlers and preschool children. It usually occurs during *the first third of night* (stage of rapid eye movement). *Autonomic manifestations* are usually minimal and *arousal threshold is high* (trials to arouse the child during the attack usually fail). In the next morning, the child *cannot recall* the event.

2. Nightmares: It is a very common condition in children. Attacks are sudden and usually occur during the *last third of night* (stage of slow wave sleep). The child screams and appears frightened but *autonomic manifestations* (tachycardia, dilated pupils and hyperventilation) are usually minimal or absent. *Arousal threshold is low* (trials to arouse the child during the attack are often successful). Within minutes the child sleeps again. In the next morning, the child often *recalls the event vividly*.

3. Night terrors: It is a more severe condition occurring in 1-3% of children. Attacks are sudden and usually occur during *the first third of night* (stage of rapid eye movement) usually between 12 Midnight and 2.00 AM. The child screams and appears frightened and *autonomic manifestations* (tachycardia, dilated pupils and hyperventilation) are frequent and pronounced. *Arousal threshold is high* (trials to arouse the child during the attack usually fail). Within few minutes the child sleeps again. In the next morning, there is total amnesia of the event and the child *cannot recall* what happened last night. This disorder should not be confused with nocturnal epilepsy.

4. Narcolepsy: It is a sudden irresistible desire to sleep that mainly occurs in adolescents. The essential feature is repetitive episodes of profound sleepiness that may occur both at rest and during periods of activity. Attacks can be long simulating epilepsy or very short (microsleeps) and misdiagnosed as attention deficit hyperactivity disorder.

5. Restless legs syndrome (RLS): This condition is characterized by uncomfortable creeping or crawling sensations in the lower limbs, which are relieved by movements. This condition results in significant delay in onset of sleep. In 80% of cases, during sleep, repetitive rhythmic kicking movements of lower limbs occur. The child is unaware of these movements but it is usually followed by significant daytime sleepiness.

6. Insomnia: It mainly occurs in adolescents and mostly related to anxiety or mood disorders as depression.

3. Habit Disorders

Thumb sucking: Normal in infants and toddlers.
Teeth grinding (Bruxism): Common in first 5 years.
Rocking and head banging: Common in toddlers.
Tics: Onset around the age of 7 years.
Masturbation: Universal in adolescent boys, less common in girls.

Habit disorders are repetitive patters of movements that can be described as habits. They are generally considered as *"tension-discharging phenomena"*. Some of them are normal at certain age groups but they are considered as disorders when they interfere with the physical, emotional or social functions.

1. Thumb sucking: This habit is extremely common in infants and toddlers and usually has no pathological significance. Older children who continue to suck thumb need evaluation. The best strategy is to ignore the problem and to give attention to more positive aspects of the child behavior. When the child tries to restrain thumb sucking, parents should encourage and praise him. The use of noxious agents as bitter salves can be used as a second-line approach.

2. Teeth grinding (Bruxism): This habit is quite common in the first 5 years and usually associated with daytime anxiety. The condition may be relieved by helping the child to reduce anxiety. Bedtime can be more enjoyable by reading or talking. Untreated conditions may cause problems with teething.

3. Rocking and head banging: This habit is common in otherwise healthy toddlers and it usually causes much anxiety and distress to parents because of the possibility of self-injury. Reassurance and support of parents is important as the condition disappears spontaneously around the age of 4 years.

4. Tics: They are involuntary repetitive muscular movements mostly of the muscles of the head and neck (as eye blinking, lip smacking and grimacing, tongue thrusting, head nodding or throat clearing). The onset is around the age of 7 years. There are 3 types or 3 grades of severity. *Simple tics* are the most common and are only involving the muscles of the head and neck. *Complex tics* are extending to limbs and trunk. *Gilles de la Tourette syndrome* is the most severe form and it is characterized by complex tics in addition to vocal tics (vocal sounds such as barking, grunting or repetition of sounds or words). Simple tics are usually transient lasting only for few weeks. Tics should be differentiated from petit mal epilepsy and other involuntary movements (as chorea).

5. Masturbation: It is probably universal in adolescent boys but less common among girls. This usually attracts attention and concern when it becomes excessive. Excessive masturbation needs investigations and psychological help. It is important to know that most infants and toddlers engage in and enjoy touching their genitalia but this is usually less common in middle childhood.

4. Anxiety Disorders

Separation anxiety disorder (SAD): Anxiety related to separation from parents.
Social phobia (SP): Anxiety in social situations.
School refusal: Refusal to go to school.
Selective mutism: Refusal to talk in front of strangers.
Panic disorder: Recurrent episodes of marked fear or discomfort.
Generalized anxiety disorder (GAD): Worries about future events or past behavior.
Obsessive-compulsive disorder (OCD): Recurrent thoughts with accompanying behavior.
Post-traumatic stress disorder (PTSD): Stress and fear following life-threatening events.

Anxiety is a normal phenomenon that has evolutionary value for the species. It has physiological component (mediated by autonomic NS) and behavioral component (worrying and wariness). Normal anxiety varies with age. Most *infants* beginning from 7-9 months show anxiety towards strangers and may show excessive clinging and difficulty during pediatric visits. *Preschool children* fears are usually related to dark, animals and imaginary situations (as ghosts). *School-age children* give up the imaginary fears of early childhood and replace them with fears of bodily harm. *Adolescents* show social anxiety and general worrying about school, friends and family.

When anxiety is excessive and interfering with social interaction and development, it becomes a disorder.

1. Separation anxiety disorder (SAD): It is characterized by unrealistic and persistent worries related to separation from parents. It is manifested by persistent avoidance to be alone or to sleep without being near the parents. They may also experience nightmares related to separation from parents or be reluctant to go to school. These children are at increased risk of developing panic disorder in adolescence.

2. Social phobia (SP): It is characterized by excessive anxiety in social situations (including school) leading to social isolation. These children and adolescent prefer to be with family members or familiar peers. However, some children show distress by their inability to engage in relationship with peers. Family history of social phobia or extreme shyness is not uncommon. Anxiolytic drugs as buspirone or alprazolam may be useful.

3. School refusal: This disorder is associated with both SAD and SP. It is a common condition occurring in 1-2% of children. Younger children usually show reluctance to separate from parents (separation anxiety) while older children show fear of exposure to unfamiliar environment or possible humiliation (social phobia). Somatic complaints as abdominal pain and headache are common. The condition is related to disturbed parent-child relationship and family disruption (as divorce and other major stresses). Many of these children have also repressive symptoms in addition to anxiety. The condition requires parental and teachers concern. Parents should reward the child for each complete school day and teachers should give special attention.

4. Selective mutism: Children with this disorder talk only at home and refuse to talk in other situations as school, daycare areas or even relative's homes. One or more stressful factors (as a new classroom or a conflict with parents or siblings) may add anxiety to this already shy child. When the disorder severely affects school performance, selective serotonine reuptake inhibitors (SSRIs) as fluxetine is effective.

5. Panic disorder: It is a syndrome of recurrent discrete episodes of marked fear and discomfort with abrupt onset of physical and psychological symptoms. *Physical symptoms* include palpitation, sweating, shaking, shortness of breath, chest pain and nausea. *Psychological symptoms* include fear of death and loss of control. Panic disorders are uncommon before adolescence with peak incidence between 15 and 19 years.

6. Generalized anxiety disorder (GAD): This disorder is characterized by unrealistic worries about future events or past behavior. The condition is commoner in adolescents with an incidence of about 2%. The onset can be sudden or gradual. This disorder needs to be differentiated from obsessive-compulsive disorder (OCD). Cognitive behavioral therapy is effective. Drugs as buspirone or selective serotonine reuptake inhibitors (SSRIs) may be added.

7. Obsessive-compulsive disorder (OCD): Obsession is a recurrent irresistible thoughts that invade consciousness and the person cannot ignore while compulsion is the accompanying behavior that aims to reduce the associated anxiety. The most common compulsions are repeated hand washing and continual checking of look or dressing. The patient commonly involves other family members in his compulsive actions. Minor obsessional thoughts as avoiding cracks in paving stones or walking under ladder is common in most children and is not considered pathological. The disorder is diagnosed when the thoughts cause distress, consume time or interfere with social functions. In 10% of cases, the symptoms are triggered or exacerbated by group A beta hemolytic streptococci (a mechanism that is similar to rheumatic chorea). This subtype of OCD is called pediatric autoimmune neuropsychatric disorder associated with streptococcal infection (PANDAS). Both cognitive behavioral therapy and Pharmacotherapy are effective. Selective serotonine reuptake inhibitors (SSRIs) are the most effective.

8. Post-traumatic stress disorder (PTSD): This disorder is characterized by considerable stress and fear following Life-threatening events that are capable to cause harm to the child or parents. The disorder is associated with behavioral and psychological sequelae resulting from the short-term and long-term effects of the traumatic events. Three groups of symptoms are essential for diagnosis: (1) *persistent re-experience* of the stressful traumatic event through intrusive or unpleasant recollection, reenactment (repeating the event) and nightmares, (2) *persistent avoidance* of reminders through isolation, amnesia and avoidance behavior, (3) *hyperarousal* through poor concentration, agitation, extreme startle response and hypervigilance (alertness especially to danger). PTSD is also related to other psychological disorders as mood disorders and behavioral disorders (see next 2 topics).

5. Mood Disorders

Major depression: Sustained lowered mood with loss of interest in usual activities.
Dysthymic disorder: Less severe but more chronic lowered mood for at least 1 year.
Bipolar disorder: Alternating episodes of depression and mania or rapid cycling of mood.

1. Major depression: This disorder is characterized by *dysphoria* (lowered mood) and *anhedonia* (obvious loss of interest and pleasure in usual activities). The condition should not be confused with sadness and unhappiness, which may occur transiently in normal persons or may accompany other psychological disorders as chronic anxiety and behavioral disorders. Major depression is characterized by sustained lowered mood, loss of interest in usual activities, low self-esteem, eating and sleeping disorders and suicidal ideas. Hallucinations and delusions may occur but they are more common in adolescents. Symptoms usually develop over several days or weeks and the duration of each episode is variable. Without treatment, the episode may persist for more than 6 months. Depression should be considered as a chronic disease marked with periods of normal mood. The incidence in childhood is 0.5-2% while is adolescence it is 0.5-8%. Many factors contribute to major depression. Genetic basis (related to serotonin reuptake) and adverse life events are clearly playing a role. Both psychotherapy and pharmacotherapy are effective. Selective serotonin reuptake inhibitors (SSRIs) as fluxetine (Prozac) is particularly effective in 70% of cases. Tricyclic antidepressants (TCAs) are not effective.

2. Dysthymic disorder: This disorder differs from depression by being less severe but more protracted. Dysphoria (lowered mood) is less severe but more chronic, for at least one year. Poor appetite, sleep problems, low self-esteem, decreased energy and feeling of hopelessness are characteristic findings. These children also show emotional and social maladjustment and appear helpless, passive, dependent and lonely. Hallucinations, delusions and suicidal ideas of major depression are absent. However, depression develops in 70% of untreated cases. The disorder is generally as common as major depression. Antidepressant pharmacotherapy is a useful treatment.

3. Bipolar disorder: This disorder is characterized by either (1) *alternating depression and mania* (i.e. alternating dysphoria and euphoria) which is commoner in adolescents and adults or by (2) *rapid cycling of mood*, which is commoner in children. Clinically, episodes of depression are alternating with euphoria, grandiose thoughts, pressured speech, distractibility, hyper-sexuality, and hyper-religiosity. In some patients, explosive aggression and hyperactivity are also present. The general incidence in children and adolescents is about 1%. The disorder may also follow major depression as 20% of patients with major depression develop manic episodes later. The disorder has genetic roots. Treatment of bipolar disorder requires the use of mood stabilizing medications. The most commonly used mood stabilizers are the antiepileptic drugs especially carbamazepine (Tegretol) and Valproic acid (Depakine). Lithium is also effective but serious side effects limit its use. Psychotherapy is ineffective.

6. Disruptive Behavioral Disorders

Breath holding attacks: Transient attacks of apnea and loss of consciousness.
Temper tantrums: Transient attacks of extreme anger.
Lying: Not telling the truth.
Stealing: Tacking properties of others in secret.
Run-away behavior: Leaving home to nowhere due to abuse or neglect.
Antisocial behavior: behavior or conduct that disrupt the society or displays hostility to it. It includes aggressive behavior, passive-aggressive behavior, conduct disorder and Oppositional-defiant disorder.

Behavioral disorders are quite common in children and they typically result from frustration and anger. Breath holding attacks, temper tantrums, defiance, lying and disobedience are quite common around the ages of 2-4 years.

1. Breath-holding attacks: These transient attacks of apnea and loss of consciousness are mainly seen in children between 2-4 years. There are two types: cyanotic and pallid. ***Cyanotic attacks*** are the common type and the attack is usually precipitated by upsetting the child. The attack starts by brief crying followed by forced expiration, apnea, cyanosis and loss of consciousness. Within a minute, breathing returns, cyanosis disappears and consciousness is regained. The attacks are benign and not life threatening. Reassurance of parents is important and no treatment is required. ***Pallid attacks***, characterized by pallor, are much less common and the attacks are usually precipitated by head trauma.

2. Temper tantrums: These attacks of extreme anger or outrage are common in toddlers between 18 months and 3 years. The attacks usually arise when the child is frustrated or when he hurts himself. Behavioral responses include screaming, crying, often with collapse to the floor and banging with legs. The child can be aggressive to other people around him but rarely injures himself. The attacks "burns themselves out" so specific intervention is not necessary. Parents should be advised to give the child time and space to recover simply by turning away briefly. Parental response by anger and shouting reinforce the defiant attitude and teach the child that "out-of-control emotions" are a reasonable and accepted response to frustration. Moreover, the children become more frightened by the intensity of the anger of their parents.

3. Lying: *In children between 2-4 years*, lying is often used as a method of playing with language or as a form of fantasy where they describe things as they wish them to be rather than as they are. *In school-age children*, lying is an effort to hide a behavior that the child does not accept in himself. Children with low self-esteem are more prone to habitual lying. Lying can be also learned from parents when the child observes that the mother and father accuse each other of lying. *In adolescents*, lying is mainly to avoid parental disapproval or as a method of rebellion. Whatever the age, when lying becomes frequent intervention is necessary.

4. Stealing: Almost all children steal something at some point of their lives. In preschool children, stealing more than one or twice is usually related to emotional deprivation and feeling of neglect. In children and adolescents, stealing can be a way for expressing anger or revenge. Like lying, stealing can be learned from adults. Parents should return back the stolen article. When stealing becomes a behavioral pattern, referral to pediatric psychiatric is necessary.

5. Run-away behavior: Although younger often threaten to run away out of frustration, actual run-away with nowhere to go is a serious disorder that necessitate psychiatric intervention. During middle childhood, most run-aways are escaping from abuse and neglect. In adolescents, disagreement with parents, abuse and neglect are the main causes. Adolescent runaways are at extreme high risk of substance abuse.

6. Antisocial behavior: It is a behavior or conduct that disrupt the society or displays hostility to it. Risk factors within the individual and family have been identified. There are different antisocial behaviors; the most important are the following:

a) Aggressive behavior: This is a serious behavior, which is commoner in males (in animals, administration of male sex hormone to females produces more aggressive behavior). The disorder has a genetic basis but environmental factors may promote aggression in susceptible children. Family unemployment, divorce, or psychological troubles within the family are correlated with aggression in children. Aggressive models in television and aggressive computer games are additional factors. Parents anger and aggressive punishment are model examples that children may imitate. These children are at increased risk of school suspension and eventual school failure. Psychiatric consultation and help are necessary.

b) Passive-aggressive behavior: Children with this disorder express their aggressive behavior passively or indirectly, mainly through stubbornness and resistance. Parents often complain that the child does not hear them and he does not respond to repeated requests. School underachievement is common in these children. These children may unconsciously adopt this behavior to gain independence, to hide low self-esteem or to control anxiety.

c) Conduct disorder: This distinct clinical entity is characterized by several different antisocial behaviors as lying, stealing, fire setting, property destruction, physical cruelty to others, cruelty to animals, repeated trials to run-away, rape and use of weapons in fighting. Diagnosis requires persistence of such behavior for at least 6 months. It is important to know that only one third of these children continue to have antisocial personality disorder in adulthood.

d) Oppositional-defiant disorder: This is a less severe behavior than conduct disorder. These children show defiance through repeated arguing, defiance of rules, blaming of others and frequent use of absence language. Some children may have mixed symptoms of three disease entities (oppositional defiant disorder, conduct disorder and attention-deficit hyperactivity disorder).

7. Neurobehavioral Disorders

Attention-deficit/hyperactivity disorder (ADHD): In 5-10% of school-age children.
Specific reading disability (Dyslexia): Unexpected reading difficulty.

School underachievement (or poor academic performance) is a very common problem in school age children. There are 8 normal neurodevelopmental functions of the brain that are necessary for learning and productivity. These eight functions are (1) Attention (concentration), (2) Memory (recalling), (3) Language (understating and speech), (4) visual ordering, (5) Sequential ordering, (6) Neuromotor functions (gross and fine motor functions), (7) Higher order cognition and (8) social cognition. Problems with one or more of these 8 functions can lead to poor academic performance.

1. Attention-deficit/hyperactivity disorder (ADHD): It is a common disorder occurring in 5-10% of school-age children and it is 3 to 4 times more common in males. It is characterized by short attention span (leading to poor school performance) and/or hyperactivity and impulsivity. ***There are 3 types***: one with predominant attention deficit, one with predominant hyperactivity and a mixed type. ***Diagnosis requires 4 criteria;*** (1) presence of suggestive symptoms for more than 6 months, (2) onset of illness before the age of 7 years, (3) significant impairment of school achievement, and (4) exclusion of other psychological disorders and other causes of school underachievement (see opposite table). There is no single cause as the condition may occur in otherwise healthy children or may follow CNS damage by infections, trauma or toxic exposure. Morphological changes in the brain have been identified including reduction in the size of corpus callosum, basal ganglia and frontal lobes. Genetic factors include abnormalities in dopamine transporter gene and human thyroid receptor beta gene. Environmental factors (as psychosocial stresses, family problems, classroom factors) may aggravate the condition but does not cause it. ***Clinical evaluation*** of these children has 4 components: (1) behavior rating scale, (2) clinical interview (to explore if the symptoms are due to ADHD or environmental factors as home or classroom stressors), (3) physical examination (to discover chronic illnesses or sensory impairment that may be the cause of school underachievement), and (4) neuropsychological examination (to evaluate intelligence and exclude mental retardation and other psychological disorders). ADHS should be differentiated from *other causes of school underachievement:* (1) chronic illnesses as bronchial asthma, allergies, diabetes, petit mal seizures, migraine headache and hematological disorders (chronic illnesses occur in 20% of children), (2) sensory impairment due to visual or hearing defects (evaluation of vision and hearing is important), (3) other psychological disorders as anxiety disorders or depression, (4) mild mental retardation (acquired hypothyroidism is an important cause that should be excluded). ***Treatment*** of these children requires medications, psychosocial intervention and behavioral training. Psychostimulants are the mainly used psychotropic drugs. The 2 available drugs are methylphinedate (Ritalin) and amphetamine (Dexedrine).

Diagnostic criteria of Attention-deficit/hyperactivity disorder (ADHD)

1. Presence of suggestive symptoms for more than 6 months

Suggestive symptoms are those of attention deficit and/or hyperactivity.
Diagnosis requires the presence of either A or B

A) 6 or more of attention deficit symptoms

1. Failure to give close attention to details or making careless mistakes in schoolwork.
2. Failure to finish schoolwork or to follow instruction.
3. Difficulty in sustaining attention in tasks or play activity.
4. Difficulty in organizing tasks and activity.
5. Avoidance or reluctance to engage in tasks that require sustained mental effort.
6. Frequent loss of necessary things for tasks (as pencils, books, tools, toys).
7. Forgetful in daily activities.
8. Easy distractibility by external stimuli.
9. Does not seem to listen when spoken to directly.

B) 6 or more of hyperactivity or impulsivity symptoms

Hyperactivity symptoms

1. Often fidgets (move around nervously) with hands or feet or squirms in seat.
2. Often leaves seat in classroom (unable to sit still, frequently walking around).
3. Often runs about or climbs excessively.
4. Often talks excessively.
5. Often has difficulty in playing quietly.
6. Often "on the go" or acts as if "driven by a motor".

Impulsivity symptoms

1. Often answers before questions have been completed.
2. Often interrupts or intrudes on others.
3. Often has difficulty awaiting turn.

2. Symptoms are present before the age of 7 years.

3. Symptoms are causing significant impairment in academic achievement.

4. Exclusion of other causes of school underachievement.

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2. Specific reading disability (Dyslexia): It is an unexpected difficulty in reading in children (or adults) who have normal mentality and adequate chances for good education. It is the most common cause of learning disabilities (LD) in children. The condition is due to difficulties in decoding and recognition of words. When the child is asked to read aloud, he displays a labored approach with hesitation, mispronunciation and repeated attempts to sound out unfamiliar words. Difficulty in spelling clearly reflects the phonologic difficulties observed in oral reading. The condition may be associated with ADHD but the two conditions are distinct separate disorders. Reading intervention programs made by experts are required with the earliest discovery of the problem. The condition should not be confused with ***stammering (or stuttering),*** which is a speech disorder commonly occurring temporarily in children between 2-4 years and is characterized by repetition of sounds, syllables and words. In 99% of cases of stammering, the condition subsides over few weeks or few months but 1% of cases turn to be persistent stammerers, which continue into school years and adult life.

8. Autism and Schizophrenia

> **Infantile autism (autistic disorder):** Impaired social relationship with compulsive behavior.
> **Childhood schizophrenia:** Psychotic disorder with hallucinations and delusions.

1. Infantile autism (autistic disorder): It is a *pervasive developmental disorder* characterized by impaired social relationships, ritualistic and compulsive behavior, and language abnormalities. The general incidence is 1/1000 and the condition is 3 to 4 times commoner in males. The illness has an onset in infancy and diagnosis can be typically made at 18 months of age. Early signs in infancy include poor eye contact, delayed smile, delay in use of words, narrow range of interest and spending hours in solitary play. Three features are essential for diagnosis: (1) *impaired social relationship* (absent or minimal eye contact, indifference to people, rarely seeking others for comfort and rarely initiating interaction with others), (2) *ritualistic and compulsive behavior* (rigid pattern of play, intense attachment to strange objects as stones and marked resistance to any change in the daily routine or environment. Tantrum-like rage and explosive outbreaks occur when change is tried, (3) *language abnormities* (delayed speech, pronoun reversal and repetition of spoken words). Other commonly present features are mental retardation, short attention span and stereotype movements as rocking, finger twirling and spinning. The cause of autism is multifactorial but genetic factors play a major role. Abnormalities in dopamine, chatecholamines and serotonine levels or pathways have been found. Treatment of autism has 4 components; promotion of normal development, reduction of stereotyped movements, removal of compulsive behavior and alleviation of family stress. Intensive behavioral therapy directed towards speech and language development is highly successful. Drugs have a minimal role but clomipramine (tricyclic antidepressant with serotonine reuptake inhibition action) is useful in reducing compulsive behavior and stereotypes. Selective serotonine reuptake inhibitors (SSRIs) seem to be effective in reducing hyperactivity and obsessive-compulsive behavior.

2. Childhood schizophrenia: It is a *psychotic disorder* characterized by disturbed thoughts, hallucinations and delusions. Social withdrawal, speech and language problems are also common and make diagnostic confusion with autism. However, the presence of hallucinations and delusions, the late onset of illness and the higher intelligence score differentiate schizophrenia from autism. Childhood-onset schizophrenia (COS) is very rare (prevalence of 1/10.000). It differs from adult schizophrenia (prevalence of 1%) by its early onset (prepubertal or early adolescence). In schizophrenic children, auditory hallucinations occur in 80% of cases but delusions and formal thought disorders do not occur until midadolescence. Childhood schizophrenia can be easily confused with mood disorders as major depression and bipolar disorder (see mood disorders). It is important to remember that mood disorders are 100 times more common than schizophrenia. The use of typical antipsychotic drugs (as haloperidol) is largely replaced by the newer atypical antipsychotic drugs (as clozapine and risperidone).

Published Books

- Pediatric Clinical Diagnosis
- Practical Pediatric Therapy
- Basic Clinical Pediatrics
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